DANUBIAN PSYCHIATRIC ASSOCIATION

psychiatria danubina

2014 • supplement 3 • volume 26

UDC 616.89

ISSN 0353 - 5053

www.hdbp.org/psychiatria_danubina

Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

1949-2014

MEDICINSKA NAKLADA
ZAGREB, CROATIA

PSYCHIAT DANUB, 26(suppl. 3): 413-554

December 2014

PSYCHIATRIA DANUBINA

An Official Journal of Danubian Psychiatric Association

Vol. 26, Suppl. 3 **December, 2014**

Acknowledgement to genuine initiative for founding Psychiatria Danubina

Prof. Dr. sc. Nenad Bohaček ***Prof. Dr. Gustav Hofmann***

Computer service: **UNIGRAF** P. Heruca 6, Zagreb

Printed by - Herstellung: **MEDICINSKA NAKLADA** Cankarova 13, Zagreb

PSYCHIATRIA DANUBINA

Psychiatria Danubina is cited/ abstracted in Excerpta Medica (EMBASE), Psychological Abstracts/ PsycINFO, Chemical Abstracts, MEDLINE/PubMed, EBSCO, Cambridge Scientific Abstracts/Social Services Abstracts, Science Citation Index Expanded (SciSearch), Social Sciences Citation Index, Social SciSearch, Journal Citation Reports/ Social Sciences Edition, Journal Citation Reports/ Science Edition, SCOPUS, BioMedWorld.com, Research Alert, Google Scholar, HRČAK, Current Contents - Social and Behavioral Sciences.

Psychiatria Danubina (ISSN 0353-5053) is published quarterly by Medicinska naklada, Cankarova 13, 10000 Zagreb, Croatia; Pro Mente d.o.o., 10000 Zagreb, Croatia.

The cost of a yearly subscription to the journal is € 50.00 for institutions, € 40.00 for individual subscribers and € 30.00 for students - the prices are without postage. (Payments in other currencies will be accepted on the basis of the official currency exchange rates). Subscriptions will be automatically renewed and the subscribes charged for it for a further period of one year, unless notification of cancellation is received by the 1st December. Advertising enquiries, correspondence and copy requests should be addressed to Prof. Miro Jakovljević, Psychiatric University Clinic, KBC Zagreb, Kišpatićeva 12, HR-10000 Zagreb, Croatia (tel: +385 1 23-88-394; tel/fax: +385 1 23-88-329).

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Printed in Croatia.

The publication of this journal is financially supported by the Ministry of Science, Education and Sport of the Republic of Croatia.

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PUBLIC AND MENTAL HEALTH

Josip Culig
Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

* * * * *

A very first definition was published at the beginning of the last century: Public health is "the science and art of preventing disease, prolonging life and promoting health through the organized efforts and informed choices of society, organizations, public and private, communities and individuals" (Winslow 1920). This statement was modified at the constitutive conference of the World Health Organization after the Second World War.

The dimensions of health can encompass "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity", as defined by the United Nations' World Health Organization (Preamble to the Constitution of the WHO 1946).

Public health incorporates the interdisciplinary approaches of epidemiology, pharmacoepidemiology, biostatistics, environmental health, community health, behavioral health, health economics, public policy, insurance medicine, occupational safety and health, and other health services. The focus of a public health intervention is to prevent and manage diseases, injuries and other health conditions through surveillance of cases and the promotion of healthy behaviors, communities and environments.

The three core public health functions are:

- The assessment and monitoring of the health of communities and populations at risk to identify health problems and priorities;
- The formulation of public policies designed to solve identified local and national health problems and priorities;
- To assure that all populations have access to appropriate and cost-effective care, including health promotion and disease prevention services, and evaluation of the effectiveness of that care.

Mental health is integral to overall health and well-being and should be treated with the same urgency as physical health. Mental illness can influence the onset, progression, and outcome of other illnesses and often correlates with health risk behaviors such as substance abuse, tobacco use, and physical inactivity. Depression has emerged as a risk factor for such chronic illnesses as hypertension, cardiovascular disease and diabetes, and can adversely affect the course and management of these conditions.

Treatment for mental disorders is available and effective. However, the majority of persons with diagnosed mental disorders do not receive treatment. The challenges for public health are to identify risk factors, increase awareness about mental disorders and the effectiveness of treatment, remove the stigma associated with receiving treatment, eliminate health disparities, and improve access to mental health services for all persons, particularly among populations that are disproportionately affected. Public health agencies can incorporate mental health promotion into chronic disease prevention efforts, conduct surveillance and research to improve the evidence base about mental health in the countries, and collaborate with partners to develop comprehensive mental health plans to enhance coordination of care (Chapman et al. 2005).

Mental health care quality of life is often regarded in terms how it is negatively affected, on an individual level, by mental disorders. Mental health medicines work also on account of meanings, expectations, images and relationships. So, treatment effectivness also depends on what patients believe how medications work and what is the nature of their problems as well as on their confidence in the physician and in the psychiatry as a whole (Jakovljevic et al. 2010)

Public health policy has a long history in Croatia

Dr Andrija Stampar, who was in 1945 one of key figures at the WHO first conference, founded School of Public Health in Zagreb in 1927. In the following years a whole network of public health organizations was erected across the country. Among them a prominent role is carried by *Public Health Institute* in Zagreb, the capital of Croatia, which was founded in 1949 as a Hygiene Institute with preventive and intervention programs focused on the urban enviroment.

In 1961 Public Health Institute became a central public health organization in the city of Zagreb, with modern public health services as epidemiology, environmental health, health statistics, health public policy, occupational and sport medicine. In 1994 school medicine service was joined, after a while also mental health, cancer screening programs, aeroallergy, pharmacoepidemiology and gerontology center.

In 2008 Public Health Institute was named after public health pioneer in Croatia, „Dr. Andrija Stampar“. Finally in this 2014, in the year of the 65th anniversary, it is rewarded as *Teaching Institute* for University students in medicine, nursing, and other health sciences.

Vision and Mission

As one of the medical excellence centers in the Republic of Croatia our vision is to be the top public health institution in the region. Our mission is to provide services in the field of public health by acknowledging the highest standards of socially responsible behavior and science-based cognitions. Our goal is to offer our customers the reliability and quality based on the principles of medical excellence.

Andrija Stampar Teaching Institute of Public Health provides services in the field of public health, epidemiology, environmental health and health ecology, clinical microbiology, school and adolescent medicine, addiction prevention and mental health care. The Institute is also a teaching base of the University of Zagreb Medical School and Josip Juraj Strossmayer University of Osijek.

We are the collaborative teaching institution of the School of Medicine Rijeka, the Faculty of Pharmacy and Biochemistry Zagreb, the University of Applied Health Sciences Zagreb and the University of Applied Sciences Velika Gorica.

Within the Institution there are four Ministry of Health Reference Centers which confirm our leading role in the Croatian public health. Our main potential is based on a large number of top experts who work as university teachers and researchers in public health projects.

Science

Scientific Unit was formed in 2001 and consists of a multidisciplinary team of 30 scientists, 15 of them achieved the scientific title according the National procedure. The collaboration on different projects with scientists and institutions in Croatia and abroad is going on. This can be followed by a regular public activity in scientific and professional journals, books, textbooks and public health manuals. Since this 2014 is our 65th anniversary, we decided to celebrate it by issuing a special edition of Psychiatria Danubina. We express special thanks to Professor Miro Jakovljevic, the Chief editor, who encouraged us and supported us in every way.

Throughout the presented papers of our scientists and their collaborators from different institutions not only do we want to emphasize the unity of public health (physical and mental), but also the need for a multidisciplinary approach to the research and what is more important, to build the solid ground for the different intervention programs in public health. For some time it was wrongly considered that mental health could not be a part of public health services but our institution proves that it is the must policy. Multidisciplinary approach is the foundation of our excellence, which can be read from the selected articles that we present here. In this supplement, we choose to present the original researches on predictors of depressive symptoms in newborns, research on depression in adolescents, research on quality of life, on the consumption of psychotropic drugs, patients' adherence to prescribed therapy, but also on nursing evaluation on diabetes self-management, dry eye in contact lens wearers and the analytical findings of antibiotics in honey.

I am convinced that those who are engaged in public health research will find useful information, while those to whom public health is not a priority of scientific research will maybe find some new scientific challenges and ideas.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 416-421 *Original paper*

MULTIVARIATE ANALYSIS OF PREDICTORS OF DEPRESSION SYMPTOMATOLOGY AFTER CHILDBIRTH

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SUMMARY

Background: *Risk factors of postpartum depression, although relatively well investigated, remain largely unclear.*

The aim of this study was to identify the most relevant predictors of postpartum depressive symptomatology that are of clinical importance using the Edinburgh Postnatal Depression Scale (EPDS) 3-5 days and 6 to 9 weeks after childbirth.

Subject and methods: *In order to explore predictors of depression, 3-5 days after childbirth, 372 participants fulfilled several questionnaires: Edinburgh Postnatal Depression Scale (EPDS), Impact of Events Scale Revised (IES-R), Big Five Inventory, and questions regarding breastfeeding practice as well as social and demographic factors. Six to nine weeks after childbirth, the same participants fulfilled the following questionnaires: IES-R, EPDS and breastfeeding practice questions.*

Results: *On a multivariate level of analysis, the predictors that increased the odds for postnatal depression symptomatology at the first study point were: unsuccessful breast feeding initiation (odds ratio (OR) 2.58; confidence interval (CI) 1.35-4.91) and personality traits neuroticism (OR 1.16; CI 1.07-1.25.). The predictors that increased the odds for depression symptomatology at the second study phase were: fear for labor outcome (OR 2.44; C1.03-5.80) and the baseline EPDS score (OR 3.32; CI 1.31-8.40). The predictor that decreased the odds at the second study phase was the personality trait Openness (OR 0.9; CI 0.86-0.99).*

Conclusions: *Immediately after childbirth biological and psychological factors seem to be predictive for postpartum symptomatology while later only psychological factors are of greater importance.*

Key words: *delivery – postpartum – depression - predictors*

* * * * *

INTRODUCTION

According to results of one of the largest meta-analysis published regarding the prediction of post-partum depression, published in the 1990s, and included 84 studies, none of the following factors were significantly associated with the development of postpartum depression in Western society: maternal age, level of education, parity, length of relationship with partner and sex of child. Thirteen significant predictors of post-partum depression were revealed: prenatal depression, self-esteem, childcare stress, prenatal anxiety, life stress, social support, marital relationship, history of previous depression, infant temperament, maternity blues, marital status, socioeconomic status, and unplanned/unwanted pregnancy (Becks 2001).

Findings suggest that various obstetrical complications (e.g. prolonged labor, stillbirth) may increase likelihood of postpartum psychosis and depression (Nonacs & Cohen 2009).

More symptoms of prenatal depression had been found in women who have been physically abused, sexual abused, institutionalized or placed in a foster family, or felt rejected by at least one parent (parental rejection) (Dayan et al. 2010). Influence of prolactin and oxytocin in the etiology of postpartum psychiatric disorders is not clear, but women that are exposed to stress postpartum or depressed, often do not breastfeed or breastfeed for a shorter period. (Henderson et al. 2003). In a recent study on 42 225 Norwegian women, results indicate that breastfeeding cessation is a risk factor for increased anxiety and depression (Ystrom 2012).

There is evidence of a connection between previous depression or other psychiatric illness with postpartum depression (Nonacs & Cohen 2009). Low extraversion and high neuroticism has been found to be connected with the development of postpartum depression (Martín-Santos et al. 2012).

The aim of this study was to find the most relevant predictors of postpartum depression symptomatology in the population of new mothers in Croatia. Data about posttraumatic stress disorder symptomatology and correlation between depression and PTSD symptomatology are presented in separate publication (in process of publishing).

SUBJECTS AND METHODS

Statistical methods

Univariate and multivariate prediction of postnatal depression were carried out by means of logistic regression, and odds ratios with 95% confidence intervals were given for each variable. Variables that, at univariate level differentiated participants by a statistical significance of less than p=0.05, were included into the

multivariate model. Differences in the prevalence of clinically relevant scores at two times the measurement were tested with the McNemar test for dependent proportions. Analyses were carried out using the SPSS 17.0 (SPSS Inc., Chicago, IL, USA) statistical software package.

Subjects

The study was performed at the Department of Gynecology and Obstetrics, School of Medicine University of Zagreb, University Hospital Centre Zagreb, Croatia.

In order to be eligible to participate in the study, the woman had to be literate, willing to fulfill the questionnaire, and have a mailing address and telephone number. Exclusion criteria included illiteracy and a known active psychiatric illness treated with psychotropic medications (affective disorders, psychosis, anxiety disorders, addiction).

In order to explore predictors of depression, a total of 372 participants fulfilled several questionnaires 3-5 days after childbirth (first phase), while 262 fulfilled the questionnaires 6-9 weeks after childbirth as described below (second phase).

Assessment

First study phase

Determination of clinically significant symptoms of depression

The Edinburgh Postnatal Depression Scale (EPDS) is a 10-item postpartum depression screening questionnaire completed by mothers and scored by clinicians (Cox et al. 1987). The score thresholds vary in various populations, and, in response, range from 7 to 16 (Hewitt et al. 2009). A validated Croatian translation was used. At the 8.5 cut-off score, the sensitivity of the scale for determining the presence of postpartum depression was 77.3%, specificity 82.4% and with a PPV of 27.9% (Nakić Radoš et al. 2013). Participants with a score ≥9 were considered to have clinically significant symptoms of depression.

Other questioners used for predictors of depression determination were

Social support as a predictor

With the author's permission, we used a 7-question questionnaire. Questions were aimed at marital status, marital problems, undesired or unplanned pregnancies and psychological difficulties from previous pregnancies (Braverman & Roux 1978).

Unfavorable family or other circumstance during participants' childhood as a predictor

The questionnaire, that was used with author's permission (Dayan et al. 2010), assessed the following factors: physical abuse, sexual abuse, institutional or foster family placement, feelings of rejection by at least one parent (parental rejection) and family secrets.

Personality traits as predictors

The Big Five Inventory (BFI) (Benet-Martínez & John 1998) questionnaire was used that consists of 44 items constructed to allow quick and efficient assessment of the 5 personality dimensions – extraversion, agreeableness, conscientiousness, neuroticism, and openness. Self-report ratings for each item were made on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). In the Croatian sample, the coefficients of internal reliability (Cronbach α) were from 0.69 to 0.80 (Hudek-Knežević & Kardum 2009).

Traumatic experience of childbirth as a predictor

To screen for PTSD symptoms, the Impact of Events Scale (revised) – Croatian (convergent validation) version (IES-R) was used. It is a 22-item self-report measure which assesses subjective distress caused by traumatic events (Weiss & Marmar 1997). The IES-R was translated and validated (convergent validation) in Croatian with a reliability of (Cronbach α) 0.91 (Ljubotina & Muslić 2003). Cut-off points of IES-R between 24 and 33 have shown both sensitivity and specificity over 70% (Çorapçıoğlu et al. 2006).

The IES-R, EPDS, BFI, Social support questionnaire, Braveman's and Dayan's questionnaires were integrated into a 9 pages questionnaire developed for the purpose of this study. Sociodemographic and health issues (complications during pregnancy, complications during and after childbirth, breastfeeding practice) were additionally addressed in our questionnaire.

Second study phase

Six to nine weeks after childbirth, the responding 262 participants which remained in the study fulfilled the following questionnaires: IES-R, EPDS and breastfeeding practice questions. Data regarding the IES-R in the second study phase is presented in separate paper.

RESULTS

Of the initial 372 women who were recruited into the study and finished the first phase, 262 returned fulfilled questionnaires by mail for the second phase of the study. The youngest mother included was 15 years of age, while the oldest was 45. The median age of the investigated 372 women was 30 (interquartile range 26-34). The sample was more educated than general population (Adamović & Mežnarić 2011): 190 participants (51.1%) had secondary school or less, 182 participants (48.9%) had higher education (bachelor, master or higher education). A total of 281 (75.9%) participants were employed, while the remaining 89 were unemployed. Missing data about employment status involved 2 participants. There were 188 primiparous women (50.5%) and 184 multiparous women (49.5%). The majority of participants, 291 (78.2%), had vaginal birth while 81 participants (21.8%) had Caesarean section. Elective Cesarean section was performed in 38 participants (10.2%) and emergency Cesarean section

(defined as obstetric emergency, where there is sudden onset of pregnancy complications during labor) was performed in 43 participants (11.6%).

Analysis of differences between responders (n=259) and non-responders(n=113) to the EPDS scale 6-9 weeks after delivery found no relevant differences in any demographic data except that responders to EPDS scale were more educated (138/259 or 53.3% university educated) than non-responders (44/113 or 38.9% university educated). Responders to EPDS were also more often employed (209/258 or 81.0%) than non-responders (72/112 or 64.3%).

In cases where patients answered the majority of questions (>80%), imputations were made on IES-R and EPDS data in order to avoid exclusion from the study (Cole 2008). Missing values were replaced by linear regression (Dayan 2010). At baseline, imputation was performed for IES-R and EPDS for 16 and 4 participants, respectively and for the second phase for 11 and 1 participant, respectively.

Phase one and phase two univariate and multivariate prediction of clinically relevant scores on the EPDS were made based on socio-demographic, biological, social and psychological factors. Variables that statistically significantly differentiated participants at the univariate level ($p<0.05$), were included into the multivariate model. Results for first and second study phase are presented in Tables 1 and 2.

At a multivariate (adjusted) level of analysis, statistically significant predictors of postnatal depression in the first phase included: unsuccessful breast feeding initiation, and personality traits neuroticism. Unsuccessful breast feeding initiation and the personality trait neuroticism increased odds for a clinically significant depression score (Table 1). The authors did not find a significant connection between clinically relevant depressive symptomatology and the following factors: age, living with other family member beside husband or children, domicile, education level, employment status, satisfaction with the income, newborn baby gender, primiparity, traumatic experience before pregnancy and childbirth, pregnancy complications, complications during and after labor. These factors were not included in the analysis.

At a multivariate (adjusted) level of analysis, statistically significant predictors of postnatal depression in the second phase included: fear of labor outcome, EPDS score at the time of delivery, and the personality trait openness. A significant EPDS score at the time of delivery and fear of labor outcome in pregnancy increased, and the personality trait openness decreased odds for a clinically significant depression score (Table 2).

Table 1. Prediction of clinically significant results on Edinburgh Postnatal Depression Scale EPDS scale 3 to 5 days after delivery (first phase)

	Clinically significant results on EPDS						Univariate		Multivariate	
	yes		no		total		OR	95% CI	OR	95% CI
	n	%	n	%	n	%				
Unfavorable family or other circumstances in childhood										
none	53	19.3	222	80.7	275	100	1		1	
one or more	23	29.9	54	70.1	77	100	1.78	1.01-3.16	1.37	0.66-2.84
Mode of delivery										
vaginal	57	19.8	231	80.2	288	100	1		1	
elective Cesarean	14	36.8	24	63.2	38	100	2.36	1.15-4.86	1.76	0.68-4.57
emergency Cesarean	12	28.6	30	71.4	42	100	1.62	0.78-3.36	1.70	0.71-4.11
Feared for labor outcome almost every day during pregnancy										
no	49	18.4	218	81.6	267	100	1		1	
yes	34	34.0	66	66.0	100	100	2.29	1.37-3.84	1.39	0.71-2.72
Lack of social support – positive responses										
none or one	69	20.8	262	79.2	331	100	1		1	
two or more	13	36.1	23	63.9	36	100	2.15	1.03-4.45	2.09	0.82-5.30
Breast feeding successful initiation										
yes	41	16.7	205	83.3	246	100	1		1	
no	40	37.0	68	63.0	108	100	2.94	1.76-4.92	*2.58*	*1.35-4.91*
Extraversion*	28	25-32	31	28-34			0.88	0.84-0.94	0.95	0.88-1.03
Agreeableness*	34	30-37	35	32-39			0.93	0.89-0.98	1.04	0.97-1.12
Consciousness*	35	31-38	37	33-41			0.90	0.86-0.95	0.97	0.90-1.04
Neuroticism*	22	19-26	18	15-22			1.18	1.12-1.25	*1.16*	*1.07-1.25*
Openness*	34	30-38	36	32-40			0.94	0.90-0.99	0.98	0.93-1.04

OR=odds ratio; 95% CI=95% confidence interval; *Median (interquartile range)

Table 2. Prediction of clinically significant results on EPDS scale 6 to 9 weeks after delivery (second phase)

	Clinically significant results on EPDS						Univariate		Multivariate	
	yes		no		total		OR	(95% CI)	OR	(95% CI)
	n	%	n	%	n	%				
Living with other family members										
yes	19	35.8	34	64.2	53	100	1		1	
no	41	19.8	166	80.2	207	100	0.44	0.23-0.85	0.53	0.22-1.25
Mode of delivery										
vaginal	39	19.7	159	80.3	198	100	1		1	
elective Cesarean	8	27.6	21	72.4	29	100	1.55	0.64-3.77	0.43	0.11-1.67
emergency Cesarean	13	39.4	20	60.6	33	100	2.65	1.21-5.79	1.79	0.58-5.57
Complications during or after labor										
no	19	16.2	98	83.8	117	100	1		1	
one or more	40	28.8	99	71.2	139	100	2.08	1.13-3.85	1.24	0.53-2.90
Feared for labor outcome almost every day during pregnancy										
no	32	17.0	156	83.0	188	100	1		1	
yes	28	38.9	44	61.1	72	100	3.10	1.69-5.70	*2.44*	*1.03-5.80*
Lack of social support– positive responses										
none or one	48	20.7	184	79.3	232	100	1		1	
two or more	12	44.4	15	55.6	27	100	3.07	1.35-6.98	1.40	0.40-4.88
Unfavorable family or other circumstances in childhood										
none	40	19.7	163	80.3	203	100	1		1	
one or more	15	34.1	29	65.9	44	100	2.11	1.03-4.30	1.45	0.55-3.85
Breast feeding										
yes exclusive	26	17.2	125	82.8	151	100	1		1	
yes with added formula	16	30.8	36	69.2	52	100	2.14	1.04-4.41	1.31	0.48-3.61
no	17	30.9	38	69.1	55	100	2.15	1.06-4.38	1.09	0.41-2.92
IES-R score 3-5 days after delivery										
not clinically significant	29	15.1	163	84.9	192	100	1		1	
clinically significant	31	45.6	37	54.4	68	100	4.71	2.54-8.75	2.03	0.82-5.06
EPDS score 3-5 days after delivery										
not clinically significant	28	14.1	171	85.9	199	100	1		1	
clinically significant	31	51.7	29	48.3	60	100	6.53	3.43-12.44	*3.32*	*1.31-8.40*
Extraversion*	29	27-33	31	28-34			0.92	0.86-0.98	1.05	0.95-1.15
Agreeableness*	33	30-38	36	32-39			0.91	0.86-0.97	0.94	0.86-1.03
Consciousness*	35	32-39	38	34-41			0.93	0.87-0.98	0.97	0.89-1.06
Neuroticism*	22	19-26	18	15-22			1.16	1.09-1.24	1.07	0.96-1.20
Openness*	33	30-38	37	33-41			0.92	0.87-0.97	*0.92*	*0.86-0.99*

OR=odds ratio; 95% CI=95% confidence interval; *Median (interquartile range)

The authors did not find significant association between depressive symptomatology and the following factors: age, domicile, education level, employment status, satisfaction with income, newborn baby gender, primiparity, previous traumatic experience, pregnancy complications. These factors were not included in the analysis.

DISCUSSION

The limitation of this study is the absence of clinical interviews during the first phase; thus the authors were not able to give the definitive clinical diagnosis of major depression, but only confirm clinically significant symptoms of depression.

Literature has shown that postpartum depression has a significant social and relational impact on mothers, their partners and offspring. Elisei et al (2013) had shown that postpartum depression can occur later than 4 weeks after delivery, contrary to DSM- IV time criteria.

The predictor of significant depression symptomatology development on both study phases, which we have found to be statistically significant on an univariate level included: unsuccessful breast feeding initiation and establishment, lack of social support, unfavorable family or other circumstances in childhood, fear for labor outcome almost every day during pregnancy, and neuroticism (increased odds), extraversion, agreeableness, consciousness and openness (decreased odds).

Lack of social support was repeatedly found to be important for depression development in other studies (Becks 2001). Similar to Dayan's study (2010) the authors found unfavorable family or other circumstances in childhood to be predictive for depressive symptomatology in both study phases.

The significant correlation between clinically significant depressive symptomatology and age, level of education, employment status, primiparity, and newborn baby gender 3-5 days after childbirth (first phase) or in 6-9 weeks after childbirth (second phase), were not found in this study, similar to Beck's (2001) meta-analysis of 84 studies. The authors did not explore other factors of socioeconomic status, such as household income, which was a relevant predictor of depression in the above mentioned meta-analysis.

Fear of labor outcome almost every day during pregnancy was also predictive for depression development on a multivariate level. In the second phase of the study, fear of labor outcome during pregnancy could be connected to anxiety. This could be explained with the Brain Derived Neurotrophic Factor (BDNF) theory of depression. Constant stress causes activation of the hypothalamic-pituitary-adrenal (HPA) axis with a corresponding increase in cortisol secretion and at excessive concentrations cortisol can suppress BDNF production (Kimpton 2012). This effect could be even more pronounced in the puerperal period and breastfeeding initiation in which the brain is influenced by various hormonal changes. Indeed, breast feeding initiation difficulty was also significant not only on an univariate, but also on a multivariate level in the first study phase. Henderson et al. (2003) found that women who were exposed to stress postpartum or depressed, often do not breastfeed or breastfeed for shorter duration. On the other hand, it was found that breastfeeding cessation is a risk factor for increased anxiety and depression (Ystrom 2012). In both study phases personality treats were connected to depression development, similarly to the Martín-Santos study (2012). In this study neuroticism was predictive for depression development on an univariate level in both study phases, but on a multivariate level neuroticism was predictive in the first phase. Additionally, the authors discovered that oppeness, as a personality trait, reduces the chance for depression development.

The authors discovered that traumatic experience of childbirth in the delivery room measured as IES-R score was predictive on an univariate level for depressive symptomatology development in the second phase of the study. On both a multivariate and an univariate level depressive symptomatology in the first phase was highly predictive for depressive symptomatology in the second phase of the study.

CONCLUSIONS

Immediately after childbirth both biological and psychological factors are predictive for postpartum symptomatology, respectively. In the period after delivery, psychological factors solely were of greater importance. Early screening for depressive symptomatology in maternity wards could help detect women at risk for development of postpartum depression.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 422-427 *Original paper*

DEPRESSION AND AUTO-AGGRESSIVENESS IN ADOLESCENTS IN ZAGREB

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SUMMARY

Background: *The aim of the study was to explore the frequency of depression among the general population of adolescents who were high school students in the city of Zagreb. As depression is associated with increased suicidal risk we wanted to check to what extent depression, as an emotional problem among youth, is associated with auto-aggression in the general population of adolescents.*

Subjects and methods: *The study was conducted on a sample of high school students in Zagreb and it included 701 students of both genders aged from 14-19 years of age. To test the depression a Beck Depression Inventory (BDI) was administered for youth between 11-18 years of age (Youth Self Report for ages 11-18). To test auto-aggression a Scale of Auto-destructiveness (SAD) was used.*

Results: *Results obtained by this study show that about 20.7% of high school students have mild and borderline depressive disorders while moderate or severe depression shows about 5% of them, whereby depression is statistically significant among girls who, on average, report more symptoms of depression. It has also been proven a significant impact of depression levels ($F(2,423)=35.860$, $p<0.001$) on auto-aggression in subjects of both genders. In both genders, moderately depressed show more auto destructiveness than those without depression symptoms ($p<0.01$). In the group of heavily depressed ($n=30$), significantly higher self-destructiveness is shown by girls ($p<0.01$).*

Conclusions: *The data suggest the importance of early recognition, understanding and treatment of depressive symptoms in adolescents in order to reduce the risk of subsequent chronic psychosocial damage.*

Key words: *depression – adolescents - auto-aggressiveness - urban populations*

* * * * *

INTRODUCTION

When depression is mentioned it is important to know that it is clinically analyzed on three levels: on the level of symptoms, syndromes and disorders; and symptomatology is observed also in a function of age and gender of the child. Although the first researches of occurrence, development and nature of depression in children and adolescents are mentioned in the works of Spitz (1965) and Bowlby (1960), it was considered for a long time that depression in children and youth cannot occur because it is hidden with psychosexual development, cognitive-emotional development, immature character or behavioral problems such as aggressiveness. In the systematic research about adolescent depression in the eighties it was observed that depressive symptoms of young adults are similar to depressive symptomatology of adults with certain specifics. The etiology of the depression in adolescence is complex, and models can be divided into two basic categories, namely biological and psychosocial. Assumed biological factors include genetic inheritance and biochemical factors, whereas psychosocial include the developmental history of the individual as well as adverse events in the environment, such as abuse and neglect and generally growing up in disadvantaged family environment. Regardless of the cause depression affects all levels of functioning of the individual and can lead to severe disturbance of normal development if it's not diagnosed and if its possible negative effects are not prevented (Rudan & Tomac 2009, Harrington 1993).

Depression among adolescents is manifested by symptoms such as low self-esteem, anhedonia, social withdrawal, fatigue, thought and attention problems, somatic disorders, self-destructive impulses, delinquent and aggressive behavior. Manifestation of depression in young people can be divided into three phenomena. For the first it is characteristic that adolescents only occasionally feel depressed mood, feel sad, moody, disappointed, miserable. Second phenomenon is the depressive syndrome, and it refers to a set of symptoms in the field of emotions and behaviors that occurs together. The third relates to the clinical view of depression with precisely defined criteria that significantly impede an individual's activities in different areas of life (Brajša-Žganec & Glavak 2002). According to the DSM-IV children and adolescents can be diagnosed with following depressive disorders: adjustment disorder with depressed mood, major depressive episode and dysthymia as the longest and most complicated disorder (APA 2000). Adolescence is considered a period of more frequent occurrence of depressive moods although

clinical depression in adolescence more often than in younger children or those before the onset of puberty, especially among girls. Approximately 5-10% of children and adolescents have experience with depressive disorders, and research suggests that the occurrence of depressive symptoms in childhood is closely associated with occurrence of depression in adulthood. Research also indicates the importance of the appearance and development of gender differences. In adolescence, the ratio of depression occurrence in boys and girls is 1:2. Regardless of the various phenomena of depression occurrence such adolescents are at significant risk of suicide, development of associated psychiatric disorders, and other medical problems (Rudan & Tomac 2009, Vulić-Prtorić 2004).

SUBJECTS AND METHODS

The research included 701 highschool students, of which one's gender was not recorded and 3 were twenty years old, which exceeded the planned age span, so their data were excluded from further investigation. The final sample consisted of 697 respondents, of which 395 boys and 302 girls. The respondents' age averaged 16.5±1.0. The respondents attended 35 classes in various Zagreb highschools (vocational and regular), where the ratio of vocational and regular classes was kept in accordance with the actual population ratio (1:3 in favor of vocational classes). The respondents' structure followed the actual ratio of the school types (1/3 regular and 2/3 vocational), while the gender distribution was in favor of boys due to the type of vocational schools involved. None of the respondents refused to take part in the research, making the turnout 100%.

Upon the obtained written permission of the Ministry of Science, Education and Sport, the headmasters of the schools in question were informed of the research. Parents were sent a written notice and the students were briefly informed about the aim, methods and procedure of the research. If both the parents and the student agreed to take part in the research, they signed a consent form. The testing was done in groups, in the classroom, during class, and lasted two classes (90 minutes). The questionnaire sequence varied in the way that in each class the sequence was moved forward by one (the last questionnaire in one class was the first in the next class, the first one became the second, etc.). Data collection was anonymous and the respondents had the right to withdraw at any moment. They were offered a possibility to talk to the examiner or to get help at any time during or after the examining.

Materials

The following instruments were used to gather the data:

- To test depression the Beck Depression Inventory – BDI was used. It is the most widely used instrument for identifying depression in the world, consisting of 21 items, the content of which is aligned with the criteria for a diagnosis of depression. Each item is a list of four statements arranged by severity of specific symptoms of depression (Beck et al. 1996).
- For auto-aggressiveness testing a standardized questionnaire, the Scale of Auto-destructiveness–SAD, was used. SAD is the instrument for measuring auto-destructive tendencies in individual's personality which is applied to respondents over 14 years of age. It consists of 107 grouped statements that make 4 subscales (suicidal depression, anxiety, aggressiveness, and borderline). The respondents' task was to answer with a YES or NO depending on whether the statement was true for them. The scales application can be individual or group, and on average it takes from 15 – 20 minutes (Dautović 2000).
- For the testing of personal, social, and school functioning as well as testing of emotional and behavioral disturbances a Youth Self Report for Ages 11 – 18 has been used The questionnaire consists of two parts. The first part refers to information about the personal, social and school functioning of adolescents. The second part contains 112 items (statements). The sum total of individual item forms eight syndrome scales (scale of seclusion, scale of physical disorders, anxiety/depression scale, social problems scale, opinion problems scale, scale of attention problems, delinquent behavior scale and the scale of aggressive behavior).

These syndrome scales are based on second-order factor analysis divided into three groups: internalizing disorders, externalizing disorders and mixed disorders, which cannot be included in any internalizing nor externalizing disorders (Achebach & Rescorla 2001).

Statistical analysis

Standard descriptive statistical methods were used for statistical and graphical data analysis (arithmetic mean, standard deviation and minimum and maximum result for normally distributed variables, and median and inter-quarter dispersion for asymmetrically distributed variables). Furthermore, the calculation of differences between groups was done with the t-test and variance analysis in cases where the variables were normally distributed and where the conditions of examined groups' variance homogeneity were met. Where the prerequisites for calculation of parametric statistical analysis were not met, a non-parametric test was used, either Mann-Whitney U test or Kruskal-Wallis test. Of the other statistical methods, multiple regression analysis was calculated. The data analysis was done using Statistical Package for Social Sciences for Windows v. 13.0 (SPSS Inc., Chicago, IL, USA) (Petz 2002, Preacher & Hayes 2008).

RESULTS

Incidence of depression

The total score was obtained by summing the items on BDI Scale. Later it was recoded into a smaller number of categories in two ways: In one case, the results are grouped in a total of 6 classes: No Depression (1-10 points), mild disability (11-16 points), marginal depression (17-20 points), moderate depression (21-30 points), severe depression (31-40 points) and very severe depression (more than 41 points). The second division is made so that the above classes are grouped into three categories: no depression (1-20 points), moderate depression (20-30 points), and severe and very severe depression (31 or more points).

The incidence of depression according to the Beck questionnaire (BDI) is shown in figure 1 and figure 2.

Figure 1 shows that mild depressive disorders has 16.1% of respondents, and 5.5% of respondents show moderate and severe depression, while the marginal depression shows 4.6% of respondents. Severe depressive disorders show 1.5% of respondents.

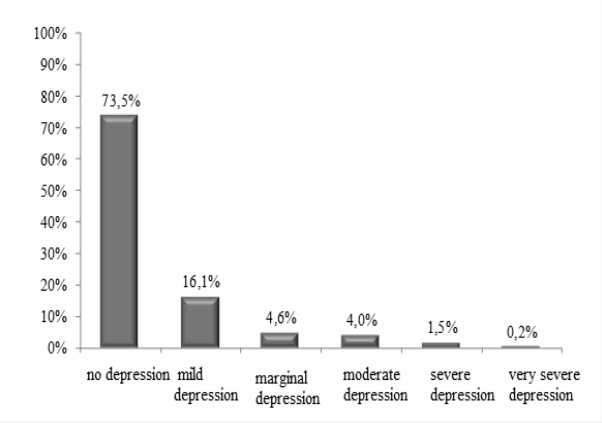

Figure 1. Classification of results on BDI questionnaire in a sample (1)

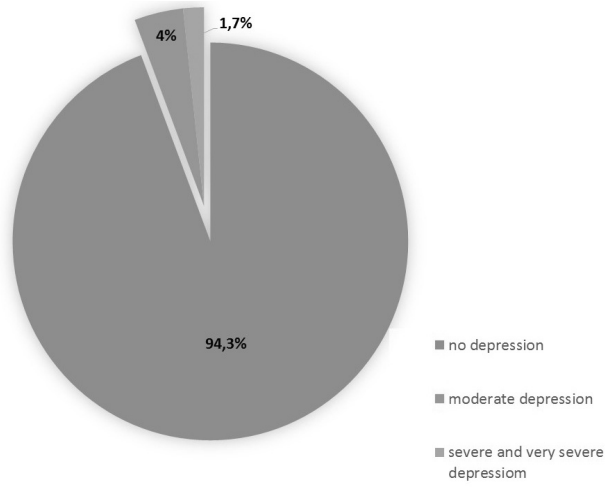

Figure 2. Classification of results on BDI questionnaire in a sample (2)

Gender differences in the average values on individual charts

T-tests for independent samples examined gender differences in the average values which subjects achieved on individual measurement charts. Where the variance did not match in homogeneity (i.e. where Levene's test was statistically significant), the value of the cases, when it is not supposed equality of variance, read „equal variances not assumed".

Average values are shown in order in figures 3, 4 and 5.

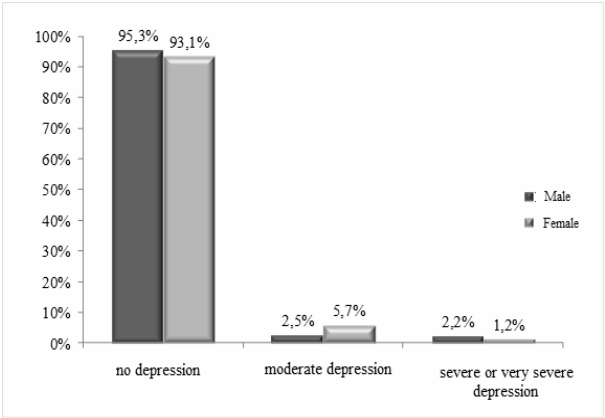

Figure 3. Classification of categories of depression by gender on BDI

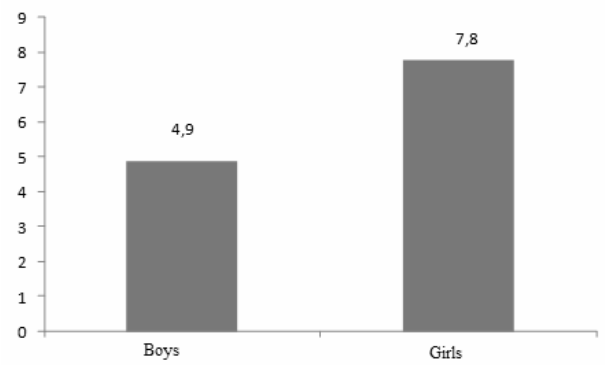

Figure 4. Average scores on the SAD depression scale considering the gender

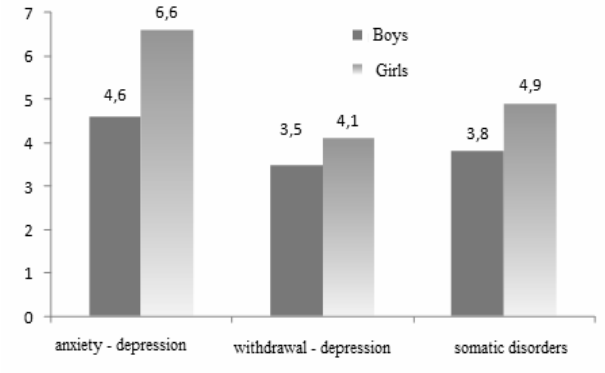

Figure 5. Average scores on the scales of anxiety-depression, depression-withdrawal and somatic disorders (Achenbach) considering the gender

The difference in achieved results on depression was statistically significant (t=5.399, df=598.1, p<0.001) in favor of girls who, on average, report more symptoms of depression.

T-test is statistically significant and shows that girls achieve higher ranking of suicidality (t=-3.809, df=637, p<0.001) compared to boys.

Girls also largely express anxiety/depression (t=6.386, df=660, p<0.001), withdrawal/depression (t=2.847, df=671, p=0.005) and somatic disorders (t=3.659, df=647, p<0.001) compared to boys. Figure 5.

Age differences in the average values on individual charts

The age variable is for this purpose recoded into two categories - one category consists of respondents from 14 to 16 years, and another from 17 to 19 years (Figure 6).

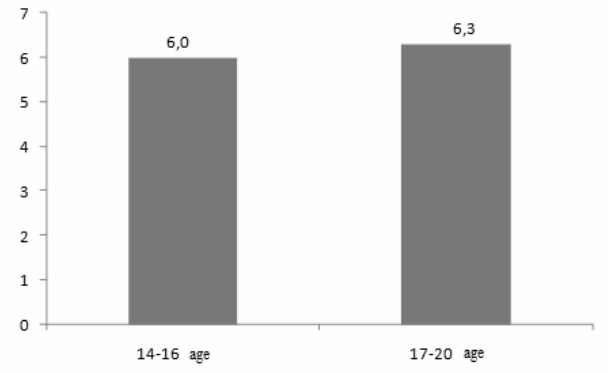

Figure 6. Average scores on the depression scale considering the age

The difference in the results achieved on the depression subscale SAD with respect to age group were not statistically significant (t=0.589, df=629, p=0.556), as well as the average scores on a scale of suicidal depression (SAD) considering the age calculated by t-test were also not statistically significant (p>0.05). Along with that, the average scores on scales of depression anxiety, withdrawal and somatic disorders (Achenbach) shows that the withdrawal/depression (t=2.300, df=449, p=0.22) was largely present in the older age group while at anxiety-depression and somatic disturbances there were no statistically significant differences.

Impact of depression on auto-aggressiveness

Bidirectional ANOVA was used to determine the effects of depression and gender as well as their interaction on the level of students' auto-destructiveness. The results are shown in Figure 7.

2x3 ANOVA shows a statistically significant main gender effect (F(1,423)=5.082, p=0.025) - girls are more auto-destructive. The effect levels of depression is also significant (F(2,423)=35.860, p<0.001). Post hoc tests showed no difference between boys and girls who do not have or have a moderate level of depression and that in both genders the moderately depressed exhibited more auto-destructiveness than those without depressive symptoms (p<0.01). In the group of severely depressed (n=30) girls shows a significantly higher auto-destructiveness (p<0.01).

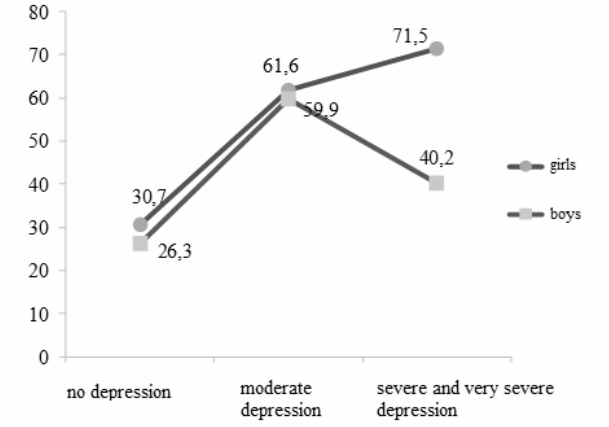

Figure 7. Average results of boys and girls in auto-destructiveness in the SAD questionnaire considering the gender and category of depression

DISCUSSION

This survey obtained results which showed that mild and borderline depressive disorders has about 20.7% of high school students while moderate or severe depression shows about 5% of the respondents, where depression was statistically significant in favor of girls who, on average, reported more symptoms of depression. This result corresponds to the epidemiological data that approximately 5-10% of adolescents have syndrome symptoms of depressive disorder. Studies show that contact with depression has around 5% of children and between 10 and 20% of adolescents. In fact, it is believed that, during adolescence, parental support, in ways of coping with negative life events, is more lacking than in relation to early childhood, and adolescence only implies greater sensitivity to stressful events (Reynolds 1994, Reynolds & Johnston 1994).

This survey also obtained the gender differences whereby girls are more depressed and report more anxiety/depression, on a scale of Achenbach questionnaire, compared to boys. This result is in accordance with studies from the literature. Some studies suggest that gender differences are caused by biological differences and even hormonal changes between girls and boys, and others believe that difference in socialization, in which girls are encouraged to be more focused on their own emotions and the analysis of them often leads to depressed mood (Halgin & Krauss Whitbourne 1994, Lewiss 2007, Brent et al. 1999).

For higher levels of the aforementioned emotional problems among girls, along with socializing and biological factors, important role plays puberty during which large hormonal changes are occurring which

generate differences in perception of themselves. Self-esteem among boys is growing because they feel stronger and bigger, and the girls are becoming dissatisfied with themselves. In addition, girls are generally more socially oriented and more dependent on positive social relationships which makes them more sensitive to the loss of friendships than boys, which therefore makes them more vulnerable to the development of emotional disorders (Mash & Barklay 2003, Rutters et al. 2008).

Exploration of emotional factors associated with auto-aggressiveness in our study showed that depression and auto-aggressiveness are significantly associated. Within both genders the moderately depressed exhibited more auto-aggressiveness than those without depressive symptoms, while in the group of severely depressed significantly more auto-aggressiveness is exhibited among girls.

Since gender differences are, in terms of emotional and behavioral problems, common finding, only differences obtained by this study and commented connection between aforementioned problems with auto-aggressiveness is presented.

Young men are more aggressive and prone to violating rules, while girls largely express anxiety and depression as well as a tendency to withdraw, somatic disorders, attention problems and other problems. For all of these problems it applies that the higher levels of emotional and behavioral problems are associated with higher auto-aggressiveness.

Age differences were also obtained. The tendency to withdraw, depressiveness and violation of the rules are largely present in the older age group. Bowlby suggested several possible circumstances that are associated with the late development of depression. His stance is in line with the theory of learned helplessness in depression, which considers that hopelessness and subsequent depression are developing when adverse events are experienced as those which cannot be controlled. In the first type of circumstances in which Bowlby (1960, 1980) states the death or loss of a parent, child feels a lack of control about the loss of caregivers and later experiences of care and/or cannot control disappointing answers addressed by the parents.

According to a study conducted in the U.S., published in May 2011., suicide is the third leading cause of death among adolescents in the U.S. and the second most common cause in the rest of the developed world which emphasizes that depressive disorder or major depressive episode is most commonly present psychiatric disorder, and is present in 35% of all suicides (Brent 2011).

Depression is the most common condition that, according to many studies conducted so far, is associated with auto-aggressive behaviors in line with self-harm and suicidal ideation where the loss of hope and a sense of hopelessness is the most powerful mediator between depression and suicidal behavior (Portzky et al. 2005, Thomson et al. 2005).

Limitations of this study derive largely from the methodology. In this study only descriptive techniques were used so the assessment of adolescents is not necessarily correct. Also, for testing of auto-aggressiveness a questionnaire was used that tendency toward auto-aggressiveness examines on the continuum.

As for the respondents, the research should definitely be carried out on a greater number of youth and children of different ages. This study was aimed at adolescents, and the differences between them and younger children can be very big. Likewise, it would be good to carry out the research on a larger sample of clinical populations. The implementation of research with participants of different age and clinical group of adolescents would give a better insight into the interrelationships of emotional, social and family circumstances associated with the development of depression. Besides, the sample of respondents on which the data was collected is made of urban population because the research was conducted in Zagreb, which is why the generalization of research is only possible with a similar population. The survey does not cover students who are excluded from school, and for them there is often a greater number of mental health problems (Laye-Gindhu & Schonert-Reichl 2005).

CONCLUSION

The results of our study indicate a large incidence of depression among adolescents. From the results of our study we can conclude that there is a relatively strong association of depression with auto-aggressive behaviors. The higher prevalence of depression among girls points to the need for a possibly different approach for girls as to boys. Certainly it would be important to sensitize the school and social services considering the importance of early recognition of these issues. The resulting data and knowledge about the serious consequences of depression indicate the importance of early recognition, understanding and treatment of adolescents with the aim of diminishing the risk of subsequent chronic psychosocial damage.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 428-434 *Original paper*

CLINICALLY SIGNIFICANT DEPRESSIVE DISORDER IN ADOLESCENCE; CROSS-SECTIONAL STUDY OF TWO CROATIAN COUNTIES

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SUMMARY

Background: *The aim of the study was to determine whether there is a difference in the intensity of depression, suicidality, and expression of clinical features among adolescents in two different regions of Krapina-Zagorje (KZ) and Split-Dalmatia (SD).*

Subjects and methods: *The study was designed as a descriptive cross-sectional, the sample consisted of 200 adolescents, 100 from each region, aging 16-18 years, from various high schools. The research was conducted by psychiatrists in Split and Krapina, where school population of Split-Dalmatia County and Krapina-Zagorje County gravitates. For the assessment of depression, the Hamilton rating scale for depression with 21 items was used, which has proven in clinical practice. For the inclusion in the study, among other parameters, participants needed to satisfy the criterion that depression is clinically significant (19 or more points on the HAMD-21).*

Results: *The data obtained points out to statistically significant difference in the intensity of depression between the two regions ($p<0.001$). There was no difference in suicidal impulses. For the most part, the expression of clinical features between adolescents in these regions showed no significant difference, except that guilt ($p=0.001$), failing in the work plan and activities ($p=0.000$) and paranoid ideas ($p=0.013$) were significantly more expressed in adolescents of Krapina-Zagorje County and sleep disorders ($p<0.001$) in adolescents of Split-Dalmatia County.*

Conclusions: *It can be concluded that depression, suicidality and much of the clinical features depend on the developmental age, i.e. the turbulent adolescent development, rather than on regional differences, although, to a lesser extent, the expression of clinical features can be influenced by milieu, lifestyle, family dynamics and educational procedures, which can partially affect the expression of clinical features.*

Key words: *depression – adolescents - regional differences*

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INTRODUCTION

Adolescence is considered a critical phase of human life due to significant changes in a person's life that occur during that period, and refer to the biological, psychological and social functioning. In the domain of social change, adolescence is a time of development in which an individual is expanding its relations outside the family into the wider social world. Relationships with parents and the environment are dramatically changing. Adolescence is generally referred to as a critical period in relation to the psychological development of the self. This period of life can be divided into: preadolescence (10-12 yrs.), early adolescence (12-13 yrs.), middle adolescence (14- 17 yrs.) and late adolescence (from 18 yrs. to the end of the functional development of the brain) (Blos 1962, Nikolić 1989, Offer et al. 1996).

Depression is one of the common medical disorders in adolescence today. It has been believed for a long time that variable and depressed mood is normal in adolescent years, but often depression first starts in adolescence and should be taken seriously. Most young people are not going through the "storm" and are considered mentally healthy (Rao & Chen 2009). Conventional wisdom, that the highest incidence of depression is in the thirties, must be reviewed, since studies conducted at the end of the last century showed a reduction trend towards ever earlier age (Haarasilta et al. 2001, Kessler & Walters 1998). The average age for the occurrence of adolescent depression is 15 years (Kessler & Walters 1998). Prevalence shows a very wide range from one study to another, and regarding the country that carried it out. The causes are the methodological differences (Thapar et al. 2012). Numerous epidemiological studies indicate that more than 8.3% of adolescents suffer from depression. Depression in adolescents is associated with a high risk of suicidal behavior. According to some studies, 7% of them commit suicide. Adolescent psychopathology is characterized by a number of dimensions that are not easily grouped into typical symptoms and only partially correspond to that seen in adults, so today anxiety in them is one of the biggest problems in psychodiagnostics. It is about psychological problems whose clinical features are extremely heterogeneous and change in the function of maturation. In adolescents, depression is described by feelings of loneli-

ness, helplessness, anger and disappointment in the family and friends who do not understand them. In clinical features, there are different changes in boys and girls in the function of age. Depression, as a disorder in the DSM-IV classification (American Psychiatric Association, 2000), is today described in a group of mood disorders, wherein the same criteria are used in diagnostics for children and adults (Birmaher et al. 1996, Fleming & Offord 1990, Mastropaolo 1972, Nikolić 1988, Nikolić 1989, Nikolić 1990, Otto 1972, Shaffer et al. 1996).

Culture is a whole which includes knowledge, beliefs, art, morals, law, customs and any other capabilities and the habits that a person has acquired as a member of society. Culture is learned and shared with others, dominates an individual who is in constant interaction with the culture, but as it affects him, forming the symptoms and characteristics, he also affects her. According to some authors, culture and not biology determines human behavior in the transitional period of life, which adolescence is. The individual is the result of cultural behavior, that shapes the personality on an ordinary, but unique way. Arabic geographer Ibn Khaldum, in the 14th century, tried to explain the differences between cultures with climate. A passionate and expressive society survive in warmer climates, while more restrained, less passionate cultures, are found in more northern climates. Since then, and probably earlier, cultural differences, regional differences, and preoccupation with them, is embedded in human consciousness and determines numerous prejudices. At the present time, under the influence of globalization, population migration, better connectivity and outermost regions, customs, values, beliefs and everything that makes a culture gradually intertwine, as one society transmits cultural features to the other (Lewis-Fernendez & Klinman 1994, Devereux 1992, Jerry 2002)

That is exactly why clinical features of depression and to what extent regional differences affect the expression of symptoms, represented the focus of our interest. The study included two different counties: one continental in the north and one coastal in the south. Marked climatic and cultural characteristics of the region result in different temperaments belonging to these areas, which we considered as to possibly be reflected on the expression of symptoms.

Aim and purpose

The aim of the study was to determine whether there is a difference in the intensity of depression, suicidality, and expression of clinical features among adolescents in two different regions of Krapina-Zagorje (KZC) and Split-Dalmatia (SDC).

The purpose of this paper is to aid development of preventive programs for adolescents with depressive disorder, and to aid prevention programs adjustment to the real requirements of our living environment.

SUBJECTS AND METHODS

Subjects

We conducted a descriptive, cross-sectional study, in two Croatian counties: Krapina-Zagorje (in the north) and Split-Dalmatia (in the south). The study included 200 participants, 100 from each county, aged 16 to 18. To ensure compatibility for age, gender and education, in every county 50 participants were female and 50 male adolescents, and the study was conducted in a variety of secondary schools: gymnasium, apprenticeship and vocational schools.

All the participants met the following inclusion criteria: being high school students, who, at the time of the study, had 16 to 18 years, who did not suffer from severe psychological or physical trauma, and who, at the time of the study, were not suffering from serious physical illness. Because they were not patients, but high school students, as well as children without chronic illness, permission for this research was provided, in accordance with applicable regulations, by the Office of the State Administration for Education and the competent authorities of the school.

Materials

Students were informed about the purpose of the study and anonymity was guaranteed to them. The form of the questionnaire contained only age and gender of the participants, without any other personal data in the questionnaire. A rating scale for depression was applied individually, using the short interview technique, focused on assessing the presence and severity of individual symptoms of depressive disorder, and after the form was filled, the number of points on the rating scale was determined. The assessment was conducted by researchers, specialists in psychiatry. When the number of 200 respondents, who represented the necessary sample size, was reached, the study was discontinued.

Assessment of depression was made based on the results of testing and scoring using the Hamilton rating scales (HAMD) with 21 items (Hamilton 1960), which has been translated and widely used in clinical practice in Croatia (Marinić et al. 2007). Its importance for adolescent psychiatry is correspondence with a comprehensive questionnaire for clinical assessment of schizophrenia and affective disorders in children and Youth K-SADS-PL, developed for the purpose of clinical studies (Williamson et al. 1992). It consists of 21 items, of which the first 17 are scored, and the remaining four are used to estimate the severity of psychotic symptoms, if present. Individual items are assessed on a scale of 0-2, and some on a scale of 0-4. Depression was assessed by examining the total number of points. The maximum number of points is 52. The result of over 23 points indicates very severe symptoms of depression, the result of 19-22 serious symptoms of depression, 14-18 medium symptoms of depression, 8-13 mild symptoms of depression, and 0-7 excludes the

presence of depressive symptoms. Depressive symptoms in mild form (8-13 points) are considered subclinical disorder, and those from 14 to 18 points on the HAMD rating scale are significant, but are less severe depressive disorders. Therefore, the focus of our interest was a major depressive episode with a score of 19 points or more on the HAMD-21 scale.

Statistical Analyses

The results obtained are presented in tables and figures. The differences will be assessed with the level of significance of 5%. For statistical data analysis, Statistica (version 7.0 SPSS Inc., Chicago, IL., USA) software package was used.

RESULTS

Results from 200 participants, aged 16 to 18, high school students from the city of Split and Krapina were processed. The average age of participants was 16.7 (SD=0.45), and respondents 16.6 years (SD=0.48). Of the total number of participants, 100 (50%) were female and 100 (50%) were male, 50 respondents from each county. The absence of depression, or its presence at a certain degree of severity, was determined by points according to HAMD-21, based on defined scoring criteria.

The test results obtained using rating scale for depression, where it is necessary to emphasize that only respondents with 19 or more points were left in this study, which represents a clinically significant depression, are summarized as follows.

The frequency of depressive disorder

See Table 1.

By analyzing the values of individual results according to the respondents, a statistically significant difference in the severity of depression was demonstrated, being assessed using a total score on the HAMD-21. In SD County the higher number of participants falls in the group of expressed depression, while on the contrary, the higher number of participants in KZ County has more than 23 points and belongs to a group with very severe depressive disorder.

The distribution of scores on the HAMD-21 for all participants

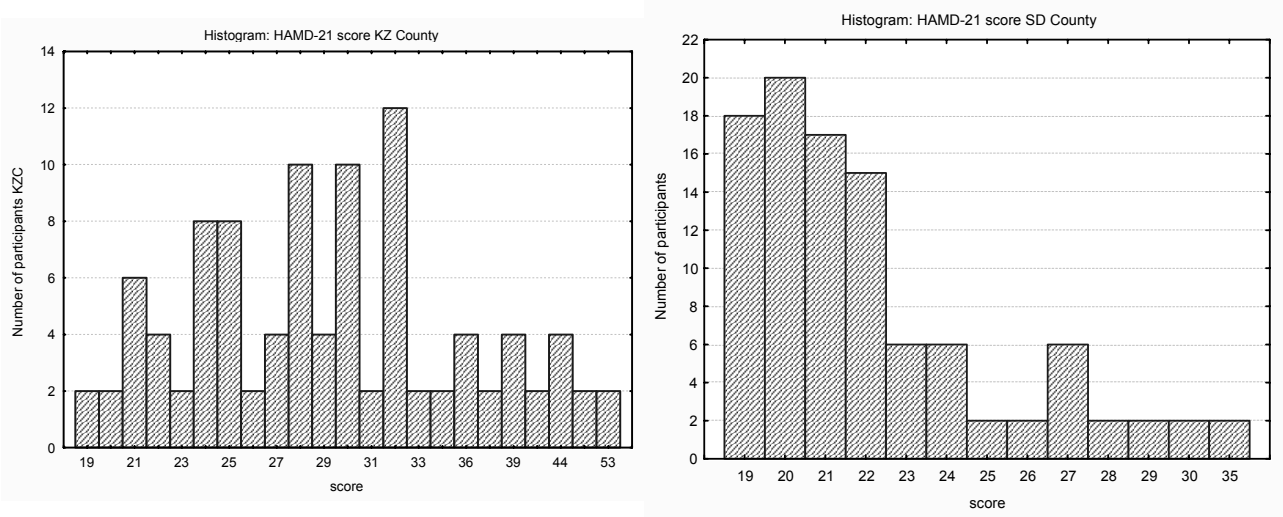
See Figure 1.

By comparing the sum of ranks, for a variable number of points on the HAMD-21, there was a statistically significant difference in the severity of depression in individual items and total (sum of ranks SDC 6433.000, sum of ranks KZC 13667.00; U-Z 1383.000 - 8.83774 at $p<0.05$) (Figure 2).

Table 1. The frequency of depressive disorder according to severity in adolescents SD County (n=100) and KZ County (n=100), based on the rating scale for depression (HAMD-21)

Estimation of severity of depressive disorder		n of adolescents according to HAMD-21 score			p*
Number of points	Severity of disorder	Total	Adolescents SD	Adolescents KZ	
		200	100	100	
19-22	serious	84	70	14	<0.05
≥23	very severe	116	30	86	

χ^2 test - χ^2=64.368 Degree of freedom (df:1) $p<0.05$; SD – Split-Dalmatia County; KZ – Krapina-Zagorje County



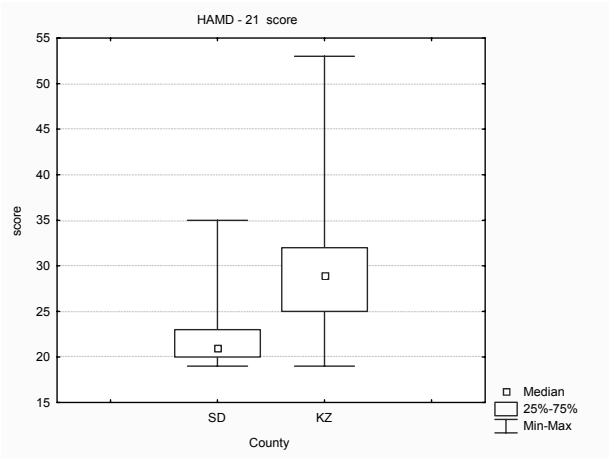
SD – Split-Dalmatia County, KZ – Krapina-Zagorje County

Figure 1. Frequency of the HAMD-21 scores in the sample, showing the distribution of scores on the HAMD-21 for participants n=100 from SD County and n=100 from KZ County

Table 2. Comparison of rank sums * per each item of HAMD-21, in all surveyed participants (n=200), by county

HAMD-21 items	Rank sum SD	Rank sum KZ	U	Z	p	Z	p	Number of participants SD	Number of participants KZ
Depressed mood	9662.00	10438.00	4612.00	-0.948	0.343	-0.991	0.322	100	100
Feelings of guilt	8729.00	11371.00	3679.00	-3.228	*0.000*	-3.585	*0.000*	100	100
Suicide	9666.00	10434.00	4616.00	-0.939	0.348	-0.971	0.332	100	100
Insomnia early	9846.00	10254.00	4796.00	-0.498	0.618	-0.558	0.577	100	100
Insomnia middle	12706.00	7394.00	2344.00	6.490	*0.000*	6.752	*0.000*	100	100
Insomnia late	10026.00	10074.00	4976.00	-0.059	0.953	-0.065	0.948	100	100
Work and activities	8238.00	11862.00	3188.00	-4.427	*0.000*	-4.570	*0.000*	100	100
Retardation: psychomotor	10547.00	9553.000	4503.00	1.214	0.224	1.303	0.192	100	100
Agitation	10004.00	10096.00	4954.00	-0.112	0.911	-0.117	0.907	100	100
Anxiety - psychic	10632.00	9468.00	4418.00	1.422	0.155	1.494	0.136	100	100
Anxiety - somatic	10182.00	9918.00	4868.00	0.322	0.747	0.351	0.725	100	100
Somatic symptoms - gastrointestinal	9876.00	10224.00	4826.00	-0.425	0.671	-0.457	0.648	100	100
Somatic symptoms - general	10270.00	9830.00	4780.00	0.538	0.591	0.592	0.554	100	100
Genital symptoms	9446.00	10654.00	4396.00	-1.476	0.140	-1.683	0.092	100	100
Hypochondriasis	9451.00	10649.00	4401.00	-1.464	0.144	-1.514	0.130	100	100
Loss of weight	9772.00	10328.00	4722.00	-0.679	0.497	-0.793	0.428	100	100
Insight	10722.00	9378.00	4328.00	1.642	0.101	1.823	0.068	100	100
Diurnal variation	10256.00	9844.00	4794.00	0.503	0.615	0.588	0.557	100	100
Depersonalization and derealization	9556.00	10544.00	4506.00	-1.207	0.228	-1.245	0.213	100	100
Paranoid symptoms	9030.00	11070.00	3980.00	-2.492	*0.013*	-2.686	*0.007*	100	100
Obsessional and compulsive symptoms	9618.00	10482.00	4568.00	-1.056	0.292	-1.154	0.248	100	100

* Mann-Witney test; SD – Split-Dalmatia County; KZ – Krapina-Zagorje County



*Mann-Whitney test; SD – Split-Dalmatia County, KZ – Krapina-Zagorje County

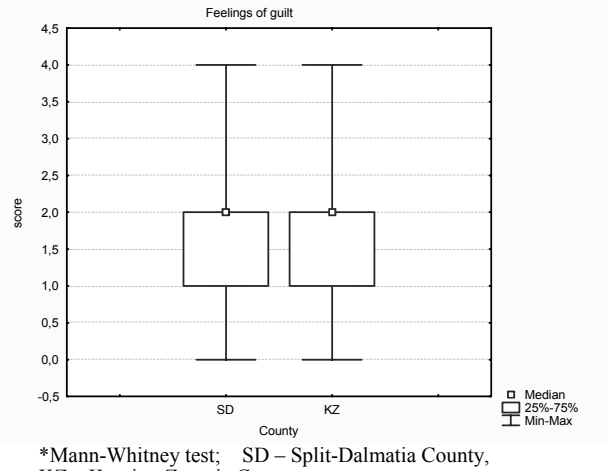
Figure 2. Box plot* by total number of points on HAMD-21, for all participants n=200, out of which a 100 is from SD County, and a 100 from KZ County

The overall analysis of results by individual particles for all participants by county

See Table 2.

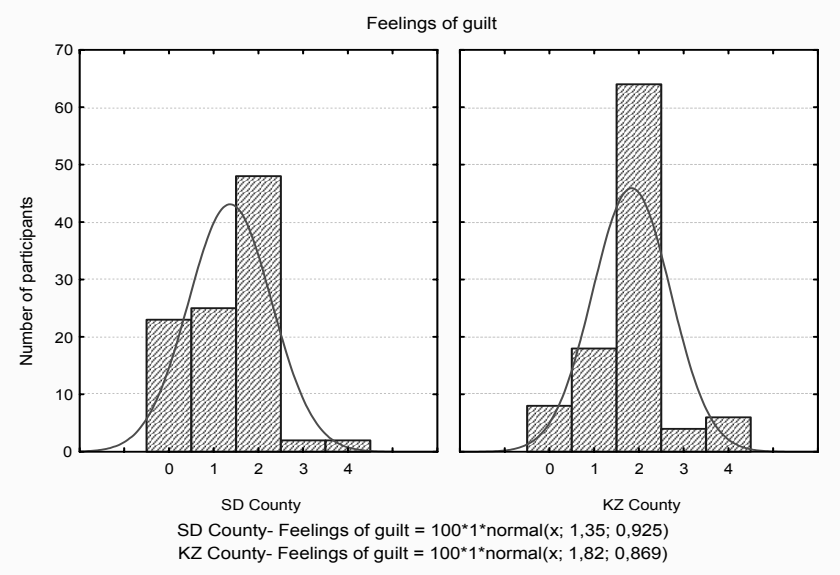
By comparing the sum of ranks, it was determined that there are statistically significant differences among adolescents from two counties in four items, namely: feelings of guilt, insomnia middle, work and activities, and quite unexpectedly, the paranoid symptoms, which belong to a group of psychotic symptoms.

By analysis of the results on the particle feelings of guilt, where rank sum analysis showed a statistically significant difference $p<0.05$ (Mann-Whitney test), box plot shows that the appearance, i.e. degree of dispersion, interquartile range, as well as the median, are completely identical (Figure 3).



*Mann-Whitney test; SD – Split-Dalmatia County, KZ – Krapina-Zagorje County

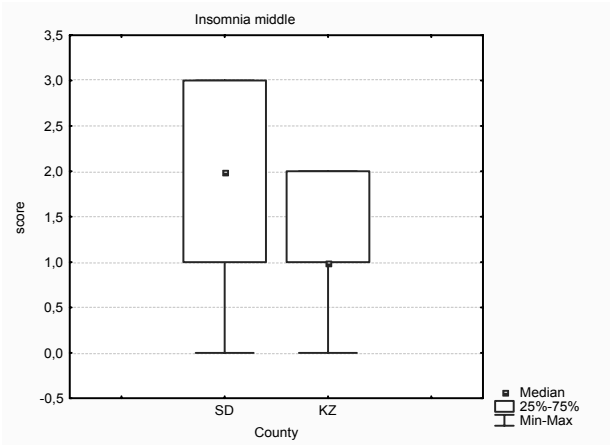
Figure 3. Box-plot* for item feelings of guilt, for all participants n=200, out of which a 100 is from SD County, and a 100 from KZ County



SD – Split-Dalmatia County, KZ – Krapina-Zagorje County

Figure 4. Frequency of the HAMD-21 scores, for item feelings of guilt, showing the distribution of scores on the HAMD-21 for participants n=100 from SD and n=100 from KZ

By analyzing the frequency of sums of points on the particle feelings of guilt, it is evident that most of the data clusters around the "2. Sense of guilt or permanent thinking about past mistakes and failures", which was checked for 48 participants from SDC, and for 64 participants from KZC. Categories "0. Feelings of guilt are not present" and "1. Self-reproach is present" are more pronounced in SDC, while the "3. Delusions of guilt and accusing or threatening voices" was more present in KZC (Figure 4).

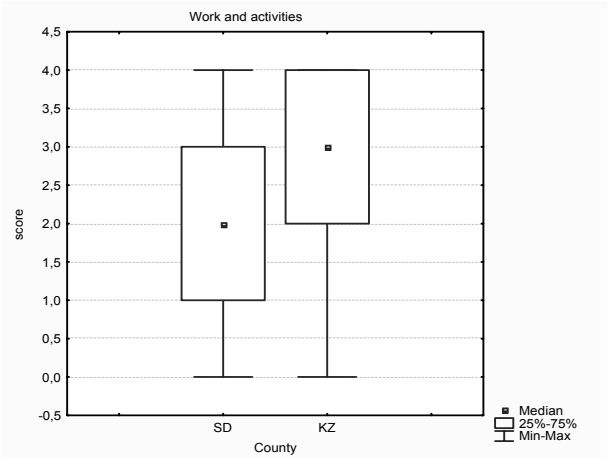


*Mann-Whitney test; SD – Split-Dalmatia County, KZ – Krapina-Zagorje County

Figure 5. Box-plot* for item insomnia-middle, for all participants n=200, out of which a 100 is from SD County, and a 100 from KZ County

By analysis of the results on the particle insomnia - middle, where the rank sum analysis showed a statistically significant difference $p<0.05$ (Mann-Whitney test), box plot shows that the degree of dispersion is higher in participants from SDC, as well as the median value, suggesting more pronounced disturbances in the field of sleep. Most of the participants complain about 1. Occasional difficulties with sleep onset and 2. Everyday difficulties with sleep onset, unlike the respondents from KZC where for the majority 0. Difficulties not present was checked (Figure 5).

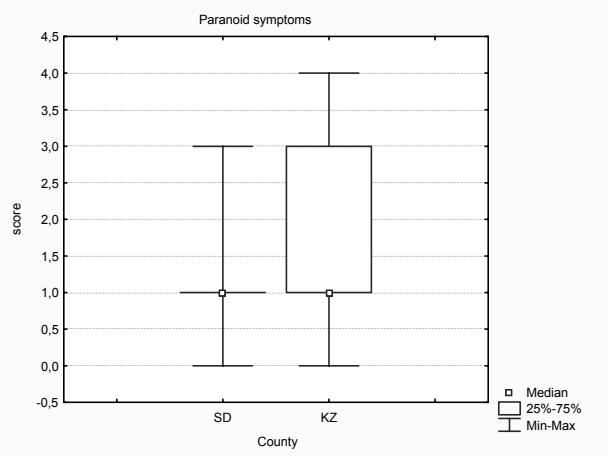
Particle Work and activities are scored 0-4, with intensity varying from 0. No difficulty, 1. A sense of incapacity, fatigue or weakness at work and leisure activities, 2. Shortening of the time required for the activity - whether it is directly or indirectly expressed in lack of agility, indecision and uncertainty (the feeling that must be forced to work and activity), 3. Shortening the time spent in activities or decrease in productivity, to 4. Termination of work because of the present illness. Significant difficulties were determined on the above mentioned particle in participants from Krapina-Zagorje County (Figure 6).



*Mann-Whitney test; SD – Split-Dalmatia County, KZ – Krapina-Zagorje County

Figure 6. Box plot*, for particle work and activities, for all participants n=200, out of which a 100 is from SDC, and a 100 from KZC

Particle Paranoid symptoms are scored 0-4 with intensity varying from 0. Not present, 1. Scepticism mild, 2. Suspicion strong, 3. Ideas of relationships are present and 4. Delusional ideas of relationships and persecution. Surprisingly, it was noticed that the presence of symptoms was found in the members of both groups of adolescents, with higher values, at the level of statistical significance, for adolescents from Krapina-Zagorje County (Figure 7).



*Mann-Whitney test; SD – Split-Dalmatia County, KZ – Krapina-Zagorje County

Figure 7. Box plot*, for particle paranoid symptoms for all participants n=200, out of which a 100 is from SDC, and a 100 from KZC

DISCUSSION

This paper compares the results of the research of expression of the clinical features, clinically significant depressive disorder, 19 and more points on the HAMD-21, between the two Croatian regions, namely: Krapina-Zagorje and Split-Dalmatia. Adolescents were all aged from 16 to 18 years, and 200 adolescents from different secondary schools in each region were tested.

Identification of clinically significant depression and intensity of difficulties by individual items, i.e. symptoms, was measured by the Hamilton Rating Scale for Depression (HAMD -21).

Once attained the size of a convenient sample, which represents a 100 adolescents (50 girls and 50 boys) from each county, who met the criteria for depressive disorder, results were analyzed and there was a statistically significant difference in the severity of depression between the two regions. Adolescents of Krapina-Zagorje County had more severe symptoms, resulting in higher aggregate scores on the applied scale. Despite the aforementioned, suicidal impulses do not show statistically significant differences between the adolescents of the two counties. Expression of clinical features, by the items, is generally the same for adolescents of both regions, except for statistically significant differences between adolescents in different counties regarding feelings of guilt (Mann-Whitney U=916.50, z=-2.299, p=0.021), insomnia - middle (Mann-Whitney U=586.00, z=4.577, p=0.000005), work and activities (Mann-Whitney U=791.00, z=-3.164, p=0.001) and paranoid symptoms Mann-Whitney U=3980,00, z=-2,492, p=0.007).

Feelings of guilt are more intense among adolescents from Krapina-Zagorje County, as well as the difficulties associated with previous work and activities. Specifically, adolescents from Krapina-Zagorje County, who meet the criteria of depression by the HAMD-21, to a greater extent are self-reproaching, they feel guilty and that they have betrayed their environment, constantly thinking about errors and omissions. In that same county, adolescents who satisfy diagnostic criteria for depression, in a higher number and more prominently have lost interest in the work and activities.

On the contrary, in the Split-Dalmatia County increasing number of adolescents who met the diagnostic criteria for depression have sleep disturbances.

Being paranoid is surprisingly present in adolescents from both counties, with statistically significant preponderance of those from Krapina-Zagorje County. One possible explanation for the prevalence of the above mentioned symptom could be sought in terms of today's living and possibility of "control" over the internet and social networks, which certainly intensifies with the increase in depressiveness.

These results cannot be compared with the results obtained in the literature, because, although numerous studies have been done on adolescent depression, no comparison of frequencies and expression of clinical features between the different regions were done so far.

These differences could be explained by differences in the milieu in which these adolescents grow up. The family and its traditions, values, attitudes, upbringing, as well as the wider environment, are affecting the development of attitudes and value systems in adolescents. Guilt is a very destructive emotion, in any case its prevalence depends on the high ideals set, which cannot be reached, criticism, the absence of praise and reward that feed and are necessary for the development of self-esteem. Patriarchal families, extended families in which the dominant role is still run by the grandparents, or one person to whom others are subordinated, the role of victim mother with an alcoholic father and authoritative husband's parents, in any case contribute to the development of guilt in children during development. Therefore, we might speculate that, although it might be the topic of the future studies, the majority of Zagorje families (which are in higher percentage rural, compared to Dalmatian ones) just have these characteristics. Another assumption could be related to the presence of participants in relation to the urban or rural area, the participants from the Split-Dalmatia County originating from more urban, tourism-oriented areas, despite the fact that children from a wider area of the county, that is not entirely urban, gravitate to high schools in Split, as well as in Krapina.

As for the differences in the work and activities, and loss of interest in previous activities, we can assume that expressed feelings of guilt affect the decline of interest and the resultant reduction in labor and activities.

Limitations of the study were the sample size (two hundred adolescents). This might make our findings less generalizable.

CONCLUSION

Adolescents from Krapina-Zagorje County and adolescents from Split-Dalmatia County differ in the expression of clinical features of depression, in feelings of guilt, difficulties in sleeping, interest in the work and activities, and paranoid symptoms. Adolescents from Krapina-Zagorje County, who meet the diagnostic criteria for clinically significant depressive disorder, to a higher extent have lost previous interest in the work and activities and have stronger and more present feelings of guilt, and a feeling of threat from its environment, while adolescents from Split-Dalmatia County to a higher extent have sleeping disorders.

The results showed that the hypothesis is partially confirmed, that compared adolescents from different regions differ in the expression of the clinical features of depression, and that they do not differ in the incidence of suicide ideation. The hypothesis, that there is no difference in the intensity of depression in adolescents from two Croatian regions, which represent the northern and southern part of Croatia, was discarded.

A special interest of researchers was raised by the fact that the study included 200 adolescents with clinically significant depression, which were "found in secondary schools" and are uncontaminated with previous treatment. Although it was not the aim of this study, all mentioned above could indicate a high prevalence of depression among adolescent population in Croatia, for which there is no systematic research, and therefore no data for comparison. Also, it supports the fact that very few people in Croatia, so far an unidentified number of them, seeks help from psychiatrists, which only confirms the need for further systematic research and improving healthcare in the field of mental health.

Acknowledgements:

We thank the Office of the State Administration for Education and the competent authorities of the school for their contribution in making this article.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 435-441 *Original paper*

LIFE SATISFACTION, OPTIMISM AND SOCIAL CAPITAL AS PREDICTORS OF MENTAL HEALTH OF THE RECIPIENTS OF FINANCIAL WELFARE FROM THE STATE

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SUMMARY

Background: *Health is largely influenced by the subjective well-being, optimism, social inclusion and satisfaction with life as well as usually defined variables. The aim of this study was to determine the relationship of dimensions of personality (optimism, control over life), social involvement (social capital) and socio-economic status with health and inequalities in health.*

Subjects and methods: *This study was performed on 1017 respondents which were chosen according to set criteria: middle age, working capability, and, according to the documentation of the Centres for social welfare, the recipients of financial welfare from the state. A questionnaire was created from several existing questionnaires with validated indicators.*

Results: *The results show that 78.1% of respondents were unemployed. Regarding the health males express a higher level of health than female. The presence of a chronic disease was found in 56.6% women and 43.4% men. The predictors of health such as optimism, life satisfaction and locus of control showed that satisfaction with life was expressed by 39.7% respondents. Greater satisfaction with life was seen in females (59.6%). Surprisingly, 47.7% of respondents said they thought they had control over their lives and decisions. Women are statistically more optimistic. Almost 60% of respondents were not satisfied with their lives.*

Conclusions: *Socially deprived population is mainly unemployed with insufficient resources for living. More burdened and higher risk for future development of the disease was found within this population. Optimism, social inclusion and life satisfaction play a large role, as protective factors in health. The interventions demand a multi disciplinary approach, and, with regard to the sensitivity of the population, the best solution is in their own empowerment, as a protective factor for mental health.*

Key words: *optimism - life satisfaction - socioeconomic status - mental health - health inequalities*

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INTRODUCTION

Pursuant to the definition of health of the World Health Organization, psychological health and social wellbeing are equally important as physical health (OECD 2012). Health is actually a dynamical process throughout man's life which can be influenced upon through individual, social, local, regional and national political involvement. Apart from the already defined variables, health is largely the outcome of the subjective feelings of wellbeing, life optimism, social inclusion and satisfaction with life. One of the unavoidable components included in the definition of health is the subjective well-being which is a predictor of mental health. Mental health has been under intensive scrutiny in the past several decades, with regard to the important role which it plays in the health of an individual and the nation as a whole. According to the Ottawa Charter for Health Promotion the basic preconditions for health are peace, a roof above one's head, education, food, income, stable eco-system, sustainable resources, social justice and equality in health (WHO 1986). According to the WHO strategy "Health for all 2020" it is defined that inequalities in health are the consequence of disparate living possibilities. Although personal responsibility which includes nutrition, physical activity, non-smoking, responsible sexual behaviour is indispensable for health, literature shows that social determinants of health are necessary for making the right decisions and right choices in life, and, consequently they are the determinants of health. Studies show that population that is low on the social ladder has twice the risk of disease and premature death (Gwatkin et al. 2007). It often causes feelings like permanent anxiety, insecurity, low self-esteem, social isolation, loss of control over life and work, long-term stress and has an important impact on health (Poortinga 2006). The impact on health is not only the consequence of material impoverishment, but also of social and psychological problems caused by life in poverty. Researches have shown that unemployment and job insecurity carries an even greater health risk, mental as well as physical (Herbig et al. 2013). The strategy "Health for all 2020" defines justice and solidarity as a basis of a healthy population. The strategy stresses that the greatest attention must be devoted to those who have the greatest needs. Researches have shown that lifestyle is a key factor in the development of a disease in as much as 50% of cases, whereas genetic factors are responsible for 20%, additional 20% are attributable to the environment which includes the complex of social and cultural conditions and physical environment, while the last 10%

cover the factor of health care (Frank WJ et al. 1994). The above determinants of disease point to a broad spectrum of possibilities of impacting the health of the population, whereby the inequalities in health can be reduced. The paradox of contemporary medicine is the choice of disease instead of health. Curative medicine, including high technology consumes 90.6% of the overall health expenses, 6.9% are devoted to the control of biological factors of health, 1.5% to the advancement of natural and social environment, and only 1.2% to the promotion of healthy lifestyles and behaviours (Bank 2013. Berkman 1995). It is known which diseases are attributable to specific factors and that lifestyle plays a large role in the morbidity of the population, as well as the living conditions of the population, and with statistical indicators we can obtain the probability of appearance of certain diseases which do not affect all persons equally. Health, except the already defined variables, is largely influenced by the subjective well-being, optimism, social inclusion and satisfaction with life. Social interconnectedness, i.e. social capital, in the researches of Michael Marmot has been emphasized as a factor equally important as is the level of control over life, and education (Marmot 2010, Marmot 2005). The relationship of life satisfaction and optimism in health was significant when mental and physical health status, social involvement, and socio-demographic characteristics were controlled for. This suggests a protective relationship between aspects of psychological well-being and physical decline in later life. The above determinants are being studied in terms of protective factors for health, as well as recovery from certain diseases. In this view, this study encompasses several dimensions which explain the determinants of inequality in health with the aim of outlining the areas which can be impacted upon in terms of reduction of the same. The dimension of the personality (optimism, control over life) and social involvement (social capital) are being looked upon in relationship with health, together with socio-economic status and inequalities (Chan et al. 2011).

SUBJECTS AND METHODS

Respondents

A total of 1017 respondents in the Republic of Croatia took part in the study. They were selected according to the following criteria: middle age, working capability, and, according to the documentation of the Centres for social welfare, the recipients of financial welfare from the state.

The target population is stratified into homogeneous groups according to predefined characteristics in order to achieve a greater efficacy in the design of the sample. The total planned number of respondents in the sample is stratified by six regions, proportionately to the square root of the number of population in each region, the size of the settlement (<2,000; 2,001-10,000; 10,001-100,000; >100,000) age and gender of the respondent. In such a way, a representative sample is ensured at the regional and national level. The source of data is the census in Croatia from 2001. The basic unit for the study was the household, and the persons who live in apartments and houses in Croatia were included into the study.

Methods-questionnaire

A questionnaire was created for the needs of the investigation. The items in the questionnaire were taken over from several existing questionnaires with validated indicators. Items connected with individual health, self-assessment of health, lifestyle, indicators of the utilization of health services and related obstacles were taken over from the Croatian Health Care Survey (HZA 2003, Ivičević Uhernik et al. 2012). The dimensions of physical functioning and limitations due to physical causes, as well as vitality, energy, changes in health and a general perception of health is based on SF 36 (Jureša et al. 2000, Ware et al. 2003). The personality dimensions were taken over from Scheier's scale of life orientation, and optimism in life from the research on life orientation (LOT - The Life Orientation Test) (Scheier et al. 1994). The items relating to measuring social interconnectedness and social inclusion were taken over from an instrument developed by Secker et al (Secker et al. 2009).

Data collection

The collection of data was carried out by means of field research in cooperation with Primary health centres, more specifically patronage nurses. Due to sensitivity, the social deprived population were interviewed by patronage nurses from their area who visit them regularly and are acquainted with the issues in the household. A total of 105 patronage nurses interviewed the respondents in their homes. On the first contact, the purpose of the study was explained to the respondents, along with the way of filling in the questionnaire and their verbal consent for participation was sought. The participation was voluntary and anonymous. A full assurance of anonymity was obtained by sending the filled questionnaires to another project team who created the database, so that the identity of the respondents cannot be connected to the questionnaire. In such a way, we ensured the respect of privacy of the respondents and bioethical standards, i.e. four basic bioethical principles (personal integrity – autonomy, justice, well-meaning and harmlessness), as well as those derived from the above (e.g. privacy, secrecy, trust and the like). All of this was in accordance with the Nuremberg Codex, the most recent revision of the Helsinki Declaration and other relevant documents.

The investigation has the approval of the Ethical Commission of the Department of Psychology at the School of Humanities and Social Sciences of the University of Zagreb and the permission of the Ministry of Social Politics and Youth.

The dependent variable

Health is the central dependent variable in this study. Bearing in mind the complexity of this phenomenon, we set out from the supposition that health is chiefly determined by the absence of chronic diseases (dimension 1), and perceived physical limitations (dimension 2), as well as the feeling of vitality (dimension 3).

Statistical analysis

For the comparison of study groups with nominal data a non-parametric and Chi-square test, i.e. the Fisher's exact test was used. The connection of nominal variables was tested by multiple logistical regression. Between the samples with ordinal data the comparison was tested with a non-parametric Mann-Whithey U-test. The level of statistical significance was set at $p \leq 0.05$. Statistical elaboration of data was done by using the STATISTICA programme (StatSoft, Inc., Tulsa, USA).

RESULTS

The study encompassed 1017 respondents who, according to the data of the Centres for social welfare are the recipients of financial welfare due to insufficient resources for living. The sample consisted of respondents of both genders; 58.1% were female (N=591) and 41.9% males (N=426), middle aged (mean 47.2, SD 11.36), of which 43.8% were married or in a relationship (N=443); 29.9% were singles (N=305). The level of education was low: 22.9% do not have a completed elementary education, and 40.7% have only elementary school (N=414). They are mostly unemployed (78.1%, N=794). The distribution according to urban (48.3%) and rural (51.7%) areas was equal (Table 1).

Table 2 shows the differences in the average result of investigated dimensions. The results show that males express a statistically significantly higher level of health than female, although the magnitude of this difference is practically negligible. The presence of a chronic disease was seen in 56.6% women and 43.4% men in the sample. As expected, age is adversely related to health so that age groups differ between them according to the average level of health; the youngest age group (25-35) has the highest, and the oldest group (50-65) the lowest values.

Individual features of the respondents (happiness, contentment, locus of control and the level of optimism) were investigated as predictors of health. In general, satisfaction with life was expressed by 39.7% respondents; statistically, greater satisfaction with life was seen in women (59.6%, $p<0.05$). Furthermore, 47.7% of respondents said they thought they had control over their lives and decisions, and here also a statistically significant difference in favour of women was seen ($p<0.05$).

Table 1. Descriptive statistics for analysing variables

	N	%	mean±SD
Gender			
Male	426	41.9	
Female	591	58.1	
Age distribution			47.26 ±11.36
25-34	153	15.0	
35-44	231	22.7	
45-54	272	26.7	
55-65	361	35.5	
Place fo living			
Rural	526	51.7	
Urban	491	48.3	
Settlement size			
Up to 2,000 habitants	430	42.3	
2,001-10,000 habitants	217	21.3	
10,001-100,000 habitants	261	25.6	
More than 100,001	109	10.7	
Education			
Without ES	233	22.9	
Elementary school	414	40.7	
Secondary school	345	34.0	
High school/Faculty	24	2.4	
Employment			
Employed full time	14	1.4	
Employed part time	12	1.2	
Unemployed to a year	42	4.1	
Unemployed over a year	794	78.1	
Retired	151	14.8	
Student	4	0.4	

The influence of health on the usual daily activities was determined by statements such as: "Did your health state cause some of the following changes in work or other daily activities in the past four weeks?" 40.1% respondents confirmed that their health had a moderate to severe influence, and the statistical calculation shows that women perceive the negative influence of health less ($p<0.05$). A personal feeling of satisfaction with life as well as the subjective feeling of control over life are, and in the assessment of health, equal in comparison with the social interconnectedness and education. The assessment of satisfaction with life was measured with the item: "When you take everything into account, how much are you satisfied with your life these days?" 59.9% of responded said they were not satisfied with their lives, and the results obtained show that women (59.6%) are more satisfied than men (40.4%) (OR=0.61; 95% CI 0.49-0.76). As regards the perception of control over life and life decisions, 47.7% of respondents said they thought they have control over their lives, and a statistically greater proportion of women said they had control over the life decisions. Personal indicators of optimism** were measured in three dimensions in which the respondents had to agree with a certain statement. The statements which point to optimism are: "In uncertain times I usually expect the best.", "I am

Table 2. Individual characteristics and personal attitudes of examinees

	Total		Males		Female			
	N=1017	%	N=426	%	N=591	%	OR	95% CI
Presence of health chronich conditions	751	73.8	326	43.4	425	56.6	0.65*	0.54-0.78
Impact of health on daily activities								
No influence	610	59.9	260	42.6	350	57.3	0.65*	0.54-0.79
Strong influence	407	40.1	166	40.7	241	59.3	0.62	0.50-0.78
Life satisfaction								
Dissatisfied	610	59.9	261	42.7	349	57.3	0.66*	0.54-0.80
Satisfied	406	39.7	164	40.4	242	59.6	0.61*	0.49-0.76
Opinion on the control of life								
In most have no	531	52.2	226	53.2	305	51.6	0.66	0.54-0.81
Have control	485	47.7	198	46.8	287	48.5	0.61*	0.5-0.75
Optimism 1**								
Agree	418	41.1	167	39.2	251	42.7	0.59*	0.48-0.74
Can't decide	271	26.6	112	26.3	159	26.8	0.66	0.51-0.86
Disagree	328	32.3	147	34.5	181	30.6	0.78	0.61-0.98
Optimism 2**								
Agree	504	49.6	200	46.9	304	51.4	0.57*	0.46-0.70
Can't decide	193	18.9	87	20.4	106	17.9	0.80	0.59-1.08
Disagree	320	31.5	139	32.7	181	30.6	0.73	0.57-0.93
Optimism2**								
Agree	602	59.2	247	57.9	355	60.1	0.59*	0.49-0.72
Can't decide	181	17.8	78	18.3	103	17.9	0.73	0.51-1.01
Disagree	233	22.9	101	23.7	132	22.4	0.73	0.56-0.97
Social capital***								
Agree	628	61.7	281	65.9	347	58.7	0.73	0.61-0.89
Can't decide	83	8.2	29	6.8	54	9.1	0.52	0.33-0.83
Disagree	306	30.1	116	27.3	190	32.2	0.56*	0.43-0.71
Social capital***								
Agree	547	53.8	230	53.9	317	53.6	0.64*	0.52-0.78
Can't decide	259	25.5	114	26.8	145	24.5	0.75	0.58-0.98
Disagree	211	20.7	82	19.3	126	21.3	0.60	0.45-0.80

* $p<0.05$; ** Optimism include three diffetent state decribed in result; *** Social capital: two different states decribed in results

always optimistic about the future." and "I expect that more good than bad things will happen to me." According to results obtained, 41.4%, 49.6% and 59.2% of respondents agreed with the statement and express optimism looking at their lives. In the breakdown according to gender it is again visible that women are statistically more optimistic ($p<0.05$). Social interconnectedness***, i.e. social capital was measured by positive, affirmative statements and the respondents had to judge whether these statements fully relate to them, or do not relate at all. According to obtained results, in the context "I have friends whom I see every week", 61.7% respondents agreed with that statement, although a statistically greater proportion of women disagree. On acceptance by friends, women are statistically more convinced that they are accepted by friends than men.

The utilization of health care includes visits to the family practitioner and specialist visits. The health system in Croatia is based on the principles of equality and justice, and the system of financing is based on the social model which presumes equal access for all citizens. 1% of the respondents do not have their family physician, 27.9% of respondents visited their physician more than ten times in the past year, and 18.3% not even once. The location of living has no influence on the use of the health services. Men visit the physician more often than women, and more than 50% of women don't remember when they were last on a preventive examination with the gynaecologist (not shown).

Table 3 shows the interrelationship of examined dimensions. According to obtained results, the strongest predictors of health are individual features: optimism, social interconnectedness and satisfaction with life, which are all in a significant correlation and mutually dependent (0.23; 0.36). Socio-economic status which is very low in this study group, is not a predictor of personal attitudes towards life, but is one of the predictors of the use of health care services and the perception of health services.

Table 3. The correlations between examined dimensions- results of the factor analysis

	Health	Optimism	Social capital	Life satisfaction	SES
Health	1	0.14	0.11	0.19	0.08
Optimism	0.14	1	0.23*	0.36*	0.06
Social capital	0.11	0.23*	1	0.21	0.07
Life satisfaction	0.19	0.36*	0.21	1	0.10
SES	0.08	0.06	0.07	0.10	1

*p<0.05

DISCUSSION

Starting out from previously stated factors of health inequalities, with this study we created an integrated description in which health (i.e. the social determination of health) is linked to the level of individual characteristics (personality), social interconnectedness (social capital) and resources (socio-economic status). The fragments of this concept and various combinations of subjective and objective variables which impact on health, were described at length in the literature about inequalities in health and health services (Judge et al. 2006, Kaplan 2007, Murray et al. 1999). The social interconnectedness, i.e. social capital has been emphasized in Michael Marmot's investigations as equally important to the level of control over life and equally important as education (Marmot 2010).

The educational status was also proved to be a significant predictor of health. Persons without completed secondary education expressed significantly lower level of health compared to those with secondary, college or university education (Eikemo et al. 2008). Bearing in mind the age differences between various groups, we may assume that age is a factor which intervenes on the above finding. Bi-variant analysis which, by contrast to multi-variant techniques, does not control the influence of age, pointed out that the employed are significantly "healthier" from unemployed and the retirees. Respondents attending school (the youngest participants in the sample), as expected, showed the highest level of health. Employment is one of the predictors of health. Long-term unemployment has a multiple influence on health. It has been established that the long-term unemployed have twice the risk of mental conditions and anxiety compared to the employed. Unemployment increases stress, and consequently the risk of a heart attack, chronic non-infectious diseases and suicide (Blakely et al. 2003). Chronic diseases are the main cause of the increase in mortality, and they are the product of socio-economic inequalities. The influence of health on usual daily activities shows the existing quality of life of a respondent. The obtained results are as expected with respect to the burden presented by health problems, and they are in accordance with previous studies.

The income of a respondent's household (divided by the number of household members) is significantly related with the expressed level of health. The examined group in this study falls into the category of socially deprived, their income is in the lowest quartiles and by that very fact they express a poorer level of health. Persons with lowest income are marked with a significantly lower level of health compared to those with higher income (Corrieri et al. 2010, Wilkinson et al. 2006). The relation between income and health is not linear, i.e. above a certain mark the growth of income stops influencing the level of health (Starfield et al. 2007). Financial status sheds light on the indirect influence of optimism and the satisfaction of life. The health status is conditioned by optimism, but it is not a precondition for satisfaction with life. Optimism is a key factor for subjective benefit, because it promotes self-esteem, harmony and a positive perception of financial conditions (Leung et al. 2005).

Social inequalities in health have been studied for a number of years and social deprivation is one of the predictors of inequality. However, in the socially deprived population too, not everyone has equal chances for the manifestation or prevention of a disease. Taking into account that various measures of the socio-economic status (SES) roughly reflect the picture of health inequalities, and that the SES gradient in health is consistent and broadly distributed, we can say that there is a number of explanatory mechanisms for the concept of influence of SES on health inequalities. Stressors and ways of coping with stress – in our concept the responses to stress correspond with the personality, and support on the part of the family and friends (social capital), lifestyle and behaviour (smoking, alcohol, physical activity and again personality). A positive attitude on life can influence health primarily by curbing negative influences of stressful life events (Ostir et al. 2001). On the other hand, researches point to a direct connection of satisfaction with life and the appearance of injuries (Koivumaa-Honkanen et al. 2000). A positive outlook on life is a protective factor in the development of the disease, such as a common cold. Cohen et al. concluded that persons with a positive outlook on life have fewer viral colds (OR=2.9, comparing bottom to top tertile). People who are optimists, have a tendency of active problem solving and facing stressful life events, while the pessimists are more prone to denial and lack of confrontation, which accumulates stress and health issues (Scheier et al.

1994). Cavelaars et al. concluded in their work that a high degree of satisfaction with life can also be an indicator how simply an individual adapts to a newly emerged situation and defines his/her achievable aims in accordance with this situation (Cavelaars et al. 1998). Research suggests that optimism is related to several health outcomes, and may improve the chances of a recovery (Matthews et al. 2004). The notion of mental welfare relates to more frequent positive experiences which include feelings such as happiness, joy, excitement, enthusiasm and satisfaction (Pressman et al. 2005).

CONCLUSION

The paper examines the level of personal capital of socially deprived population, both in relation to health and the utilization of health services. Socially deprived population is mainly unemployed, with a larger number of persons per household and insufficient means of livelihood. For this reason, they receive support from the state but, in spite of this their income is in the lower quartile of income in the country. The level of education is also low, and the possibility of finding a job in times of economic crisis is very slim. In accordance with the above, they have a very low socio-economic status. Consequently, they are more burdened with health issues and carry a greater risk for the emergence of new health issues. On the other hand, optimism, social inclusion and satisfaction with life, as protective factors in health, play a large role and are connected with one another. Socio-economic status has no impact on the personal outlook on life. However, it has an impact on the satisfaction with life and the health state load. Social inclusion is also a protective factor, but only in cases where the socio-economic conditions are acceptable. In socially deprived population, the interventions demand a multi-disciplinary approach, and, with regard to the sensitivity of the population, the best solution is in their own empowerment, as a protective factor in mental health.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 442-449 *Original paper*

PSYCHOLOGICAL AND SOMATIC HEALTH PROBLEMS IN BOSNIAN REFUGEES: A THREE YEAR FOLLOW-UP

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SUMMARY

Background: *Aim of this study was to explore association between psychiatric disorders (PTSD and depression) and chronic medical illnesses in a group of Bosnian refugees followed up for three years (1996-1999).*

Subjects and methods: *Study was conducted in refugee camps in Varaždin, Nbaseline=534, Nendpoint=376 (70.4%). The interviews were conducted in Bosnian, data on depression and PTSD were collected using the Hopkins Symptom Checklist-25 and Harvard Trauma Questionnaire, respectively. Medical conditions were self-reported.*

Results: *Most important findings: 1) Half of the sample at both study points reported no psychiatric problems (N=294, 55% vs. N=225, 59%), others suffered from depression (N=99, 18.5% at both times), PTSD (N=30, 5.6% vs. N=15, 4%), and depression + PTSD (N=129, 24.2% vs. N=114, 30.3%); 2) A total of 15 medical conditions were identified, and most frequently present were high blood pressure (N=201, 37.6%) and heart disease (N=167, 31.3%); 3) Occurrence of medical conditions was related to the clinical group – they were more frequent in subjects diagnosed with depression and depression + PTSD, than in those who were asymptomatic or suffering from PTSD only.*

Conclusions: *Our data indicate the persistence of both psychological and somatic health problems in Bosnian refugees involved in this study over time. Holistic approach and avoiding of mind-body dualism might be beneficial for the care and long-term prognosis of these people.*

Key words: *posttraumatic stress disorders – depression - medical illnesses – refugee - longitudinal study*

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INTRODUCTION

United Nations Convention Relating to the Status of Refugees (1951) defines a refugee as "someone who is unable or unwilling to return to their country of origin owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group, or political opinion". What characterizes life of refugees are traumatic experiences and violence connected to war in countries of their origin, together with cultural shock, problems with adaptation as well as acculturation after arriving to host countries (Ferren 1999).

Due to all these facts, there is a large interest for psychological sequelae of war, such as posttraumatic stress disorder and possible comorbidity with other psychiatric disorders as well as different medical conditions in population exposed to war trauma. PTSD is an anxiety disorder, characterised by intrusive re-collections, emotional numbing, avoidance behavior, and symptoms of vegetative hyperarousal, developed after exposure to extrem traumatic events (APA 1994, WHO 1994). As war is one of the most horrific human experiences characterized with long lasting and complex traumas and multiple losses (home, loved ones and ideals), PTSD is often accompanied by prolonged grief, and at the end with depression (Momartin et al. 2004). During clinical treatment of patients with PTSD, high incidence of other disorders were observed which encouraged investigation of comorbid conditions (Kozarić-Kovačić et al. 2000, Mollica et al. 1993, Mollica et al. 1997, Mollica et al. 1988). These investigations showed that depressive disorder, bipolar disorder, and other anxiety disorders as well as abuse of alcohol are most common diagnoses that accompany PTSD. Comorbidity of PTSD and depression was shown in studies of the refugee adult population (Mollica et al. 1999, Mollica et al. 2001, Klarić et al. 2007, Momartin et al. 2004), as well as in refugee children during and in the post-war period. (Stein et al. 1999, Thabet et al. 2004, Hasanović et al. 2006). There is a large interest in investigating comorbidity of PTSD and physical health problems, as well as comorbidity of depression and physical health problems. There is a growing literature on impact of extended stress on physical health in refugees (Kinzie et al. 1990, Kinzie et al. 2008, Gregurek et al. 1998, Kadojić et al. 1999) as well as in general population (Goodwin & Davidson 2005, Hezler et al. 1987), and it

is more and more obvious that there is a connection between diagnosed PTSD and somatic disorders, as well as with depression (Miranda et al. 2002). Kadojić et al. (1999) investigated the impact of traumatic experience of war sufferers on cerebrovascular disease and found that total risk for stroke was higher in the exposed group. Gregurek et al. (1998) investigated change in pulse rate among civilians during air-raid and concluded that there was no adaptation to a traumatic war situation, as civilians reacted with incrised pulse frequency at every moment of the air-raid sound. In their retrospective study Bergovac and al. (2005) examined the effects of war in Bosnia and Herzegovina on the occurrence of acute coronary syndrome among civilians. Results had shown that in five year period during the war, the common population had increased numbers of acute myocardial infarction and unstable angina pectoris cases. In the long term follow-up of the prevalence of essential hypertension in the family members of soldiers killed during the war in Bosnia and Herzegovina, Šantić et al. (2006) showed higher rates than in the families without killed relatives.

Due to the war in Bosnia and Herzegovina, a large number of refugees came to the Republic of Croatia in the course of 1992 to 1995. In the summer of 1991, the number of displaced persons and refugees in Croatia was 90.000, and in October the same year it was 400.000 (Lang 1993). There are studies dealing with PTSD and its sequelae on Bosnian refugees. In 1996, we reported initial findings of a study of Bosnian refugees, demonstrated an association between psychiatric disorders (depression and posttraumatic stress disorder) and disability in a refugee population (Mollica et al. 1999). The goal was to assess the degree of disability associated with trauma and other risk factors, the relationship between psychiatric symptoms (depression and PTSD) and disability, and the relation between chronic medical illnesses and disability. In 1999, those who were still living in the region and the families of those who died were re-interviewed, and the next report was done. That report investigated the association between psychiatric disorders (depression and PTSD), disability, and other baseline risk factors with follow up status, chronicity of psychiatric disorders and disability and their relationship at both points in time, and risk adjusted association of psychiatric disorders and disability with the likelihood of mortality and emigration (Mollica et al. 2001).

In this study, our aim is to explore the association between psychiatric disorders (PTSD and depression) and chronic medical illnesses in a group of Bosnian refugees who were followed up over three years.

SUBJECTS AND METHODS

In 1992, Croatian government established, among others, refugee camps in Varaždin, Northeastern Croatia. In the same year, NGO Ruke from Zagreb, Croatia began providing counseling and other psychosocial services to camp residents.

In 1996, Ruke and the Harvard Program of Refugee Trauma interviewed 573 adults from families, totaling 1275 people, living in Varaždin camps. In 1999, the Harvard Program in Refugee Trauma and 9 members of the original interviewing staff located and re-interviewed all the original respondents still living in the region and families of the deceased. The re-interview followed procedures established in the baseline study (Mollica et al. 1999). Study design and inform consent procedure was approved by the Human subjects committee of the Harvard Medical School as well as by Ethical Committee, Clinical Hospital Center Zagreb. The interviews were conducted in Bosnian, took approximately 90 minutes per person and they consisted of interviewers explaining the purpose of the study, together with reading the text with an explanation of confidentiality, anonymity and voluntary participation. The participants were told that they could choose not to answer specific questions. Each interview included the Hopkins Symptom Checklist 25 (HCSL 25) (Mollica et al. 1987) and Bosnian version of the Harvard Trauma Questionnaire (HTQ) (Mollica et al. 1992, Oruc et al. 2008).

The HCSL 25 is a 15 item scale used to assess depressive symptoms, and the HTQ contains a scale consisting of 16 of 17 diagnostic criteria for PTSD as defined in DSM IV. As described in previous reports, scale cutoff points have not been established in this population, and an algorithm method was selected that replicated DSM IV criteria for diagnosis of depression (HCSL 25) and PTSD (HTQ) (Mollica et al. 1987, Mollica et al. 1992, Oruc et al. 2008, Klejin et al. 2001).

We required a positive response, three or four on the HCSL 25, on either depressed mood or diminished interest or pleasure, and at least four of six DSM IV Criterion A symptoms (significant weight loss or change in appetite, insomnia or hypersomnia, fatigue or loss of energy, feelings of worthlessness, diminished ability to think or concentrate, and recurrent thoughts of death) (APA 1994). Observable psychomotor agitation or retardation, which is also criterion A symptom, was omitted because interviewers did not conduct a mental status examination in this study. For PTSD, the DSM IV algorithm included a positive response, 3 or 4 on the HTQ, on at least 1 of the re-experiencing symptoms from criterion B, at least 3 of the 7 avoidance and numbing symptoms from criterion C, and at least 2 of the 5 arousal symptoms from criterion D. Exposure to a traumatic event, which is criterion A, was deemed to have been met by all respondents (Mollica et al. 1999, Mollica et al. 2001).

Medical conditions for this study are defined as self-reported history of high blood pressure, heart disease, stroke, cancer, anemia, tuberculosis, diabetes, arthritis, duodenal or ventricular ulcer, asthma, cirrhosis or liver disease, alcohol or drug abuse, gynecological disorder, epilepsy. The subjects were asked in the (self-report)

questionnaire if their doctor ever told them that they suffered from any of the listed conditions, due to the fact that at that point of time they could not have medical records.

For statistical analysis, SPSS version 17.01 (SPSS, Inc., Chicago, IL) (1998) software was used. Chi-square test was used to compare differences between groups of nominal variables and Mann Whitney U or Kruskal-Wallis for assessing differences between ordinal variables. The level of statistical significance was set to α=0.05.

RESULTS

Study sample consists of 534 subjects (Nbaseline = 534, Nendpoint =376, 70.4%), mostly women (N=315, 59%) in 35-54 age group (N=181, 33.9%), married (N=252, 47.2%), unemployed (N=315, 83.3%) and without formal education (N=197, 36.9%). General characteristics are given in Table 1. The endpoint sample differs only in age due to the fact that population was older after three years (chi square=12.38, df=3, p=0.006).

Baseline data (year 1996) suggests that half of the sample had did not qualify for any psychiatric disorder (N=294, 55%), while 99 subjects (18.5%) met criteria for the diagnosis of depression and 30 subjects (5.6 %) for PTSD. A total of 110 respondents (20.6%) were diagnosed with both, depression and PTSD. In 1999 the results were very similar - 225 subjects (59%) were asymptomatic, 86 (22.8%) met criteria for the diagnosis of depression and 15 for PTSD (4.0%). A total of 52 respondents (13.8%) met criteria for the both, depression and PTSD (Table 2). Our results indicate that large proportion of our sample suffered from comorbid medical conditions. A total of 15 medical conditions were identified, and most frequently present were high blood pressure (N=201, 37.6%) and heart disease (N=167, 31.3%). Their distribution across the four clinical groups (asymptomatic, depression, PTSD, depression + PTSD) does not follow a normal distribution (e.g. blood pressure, Kolmogorov-Smirnov=0.41; df=529; p<0.01). Our results indicate that number of medical conditions is related to the clinical group (Kruskal Wallis =95.8; df=3; p<0.01), separate Mann Whitney U tests show the difference and direction of difference between groups: medical conditions were more frequent in subjects diagnosed with depression, and depression together with PTSD, than in those who were asymptomatic or suffering from PTSD only. For details see Table 3.

Table 1. Study sample, N (%)

	Baseline N=534 (100%)	Endpoint N=376 (70.4%)	Statistics
Gender (F/M)	315 (59.0)/219 (41.0)	266 (63.0)/156 (37.0)	χ^2=1.62; p=0.203
Age categories (years)			
18-34	105 (19.7)	49 (13.0)	
35-54	181 (33.9)	137 (36.2)	χ^2=12.36; p=0.006
55-64	137 (25.7)	85 (22.5)	
65+	111 (20.8)	107 (28.3)	
Marital status			
married	252 (47.2)	179 (47.4)	
separated/divorced	65 (12.2)	34 (9.0)	χ^2=5.27; p=0.153
widowed	118 (22.1)	100 (26.5)	
never married	91 (17.0)	52 (13.8)	
Ethnicity			
Bosnian Muslim	320 (59.9)	210 (55.9)	χ^2=3.69; p=0.158
Croat	180 (33.7)	148 (39.4)	
Other	33 (6.2)	17 (4.5)	
Education			
no formal education	197 (36.9)	150 (39.9)	
primary school (8 yrs.)	113 (21.2)	90 (23.9)	χ^2=3.16; p=0.368
high school (12 yrs.)	148 (27.7)	89 (23.7)	
university (14 yrs. or more)	76 (14.2)	47 (12.5)	

Table 2. Psychiatric disorders*, N (%)

	Baseline N=534 (100%)	Endpoint N=376 (70.4%)	Statistics
No symptoms	294 (55.1)	225 (59.5)	χ^2=2.061; p=0.151
Depression	99 (18.5)	86 (22.8)	χ^2=2.558; p=0.110
PTSD	30 (5.6)	15 (4.0)	χ^2=1.245; p=0.265
Depression + PTSD	110 (20.6)	52 (13.8)	χ^2=6.910; p=0.009

* Algorithm method was selected that replicated DSM IV criteria for diagnosis of depression (HCSL 25) and PTSD (HTQ) (ref 26, 27, 28)

Table 3. Difference in total number of clinical conditions due to respondent's psychical symptoms

Clinical groups - tested pairs	Z	P	Mean rank (1)	Mean rank (2)
Asymptomatic-depression	-7.30	<0.001	asymp 173.36	dep 267.21
Asymptomatic –depression and PTSD	-8.17	<0.001	asymp 174.18	dep&ptsp 278.19
Depression - PTSD	-3.01	0.003	dep 70.39	ptsp 47.22
PTSD - depression and PTSD	-3.36	0.001	ptsp 48.68	dep&ptsp 76.45
Asymptomatic - PTSD	-1.64	0.101	asymp159.87	ptsp 188.23
Depression – depression and PTSD	-0.54	0.588	dep 102.64	dep&ptsp 107.13

Table 4. Depression and asymptomatic respondents*

	Baseline N=534 (100%)				Endpoint N=376 (70.4%)			
Comorbid medical conditions	Depression 99 (18.5)	Asymptomatic 294 (55.0)	χ^2	P	Depression 86 (22.8)	Asymptomatic 294 (55.0)	χ^2	P
High blood pressure	53 (53.5)	80 (27.2)	22.92	<0.001	56 (65.1)	61 (27.4)	37.62	<0.001
Heart disease	45 (45.5)	51 (17.3)	31.70	<0.001	45 (52.3)	49 (22.0)	27.01	<0.001
Anemia	36 (36.4)	42 (14.3)	22.69	<0.001	26 (30.2)	40 (17.9)	5.59	0.018
Arthritis	32 (32.3)	48 (16.3)	11.69	0.001	44 (51.2)	57 (25.6)	18.49	<0.001
Kidney disease	23 (23.2)	36 (12.2)	7.01	0.008	25 (29.1)	32 (14.3)	8.94	0.003
Asthma	24 (24.2)	33 (11.2)	10.12	0.001	17 (19.8)	20 (9.0)	6.87	<0.009
Ulcer	26 (26.3)	29 (9.9)	16.55	<0.001	10 (11.6)	8 (3.6)	7.31	0.007
Stroke	14 (14.1)	14 (4.8)	9.85	0.002	3 (3.5)	5 (2.2)	0.38	0.536
Diabetes	12 (12.1)	14 (4.8)	6.49	0.011	14 (16.3)	10 (4.5)	12.05	0.001
Liver cirrhosis	7 (7.1)	14 (4.8)	0.78	0.377	3 (3.5)	3 (1.3)	1.50	0.221
Gynecological	11 (11.3)	21 (7.1)	1.71	0.191	7 (10.9)	12 (9.0)	0.20	0.658
Tuberculosis	3 (3.0)	7 (2.4)	0.13	0.723	5 (5.8)	5 (2.2)	2.53	0.112
Cancer	3 (3.0)	5 (1.7)	0.66	0.418	2 (2.3)	4 (1.8)	0.09	0.761
Seizure	6 (6.1)	4 (1.4)	6.60	0.010	1 (1.2)	4 (1.8)	0.16	0.694

*Psychiatric status was determined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition algorithm as described in the text. Medical conditions for this study are defined as self -reported history as described in the text

Table 5. PTSD and asymptomatic respondents*

	Baseline N=534 (100%)				Endpoint N=376 (70.4%)			
Comorbid medical conditions	PTSD 30 (5.6)	Asymptomatic 294 (55.0)	χ^2	P	PTSD 15 (4.0)	Asymptomatic 294 (55.0)	χ^2	P
High blood pressure	9 (30.0)	80 (27.2)	2.89	0.089	4 (26.7)	49 (22.0)	0.18	0.672
Heart disease	12 (40.0)	51 (17.3)	2.19	0.139	6(40.0)	61(27.4)	1.11	0.292
Anemia	4 (13.3)	42 (14.8)	0.18	0.671	4(26.7)	57 (25.6)	0.09	0.924
Arthritis	4 (13.3)	48 (16.3)	0.02	0.887	3 (20.0)	40 (17.9)	0.04	0.841
Kidney disease	5 (16.7)	36 (12.2)	0.48	0.488	4 (26.7)	32 (14.3)	1.66	0.197
Asthma	6 (20.0)	33 (11.2)	1.98	0.159	4 (26.7)	20 (9.0)	4.86	0.028
Ulcer	5 (17.2)	29 (9.9)	7.43	0.006	0 (0.0)	5 (2.2)	0.34	0.560
Stroke	1 (3.3)	14 (4.8)	1.38	0.240	1 (6.7)	8 (3.6)	0.37	0.545
Diabetes	1 (3.3)	21 (7.1)	0.13	0.723	2 (13.3)	3 (1.3)	9.81	0.002
Liver cirrhosis	1 (3.3)	14 (4.8)	0.13	0.723	1 (6.7)	10 (4.5)	0.15	0.697
Gynecological	3 (10.0)	21 (7.1)	0.32	0.569	0 (0.0)	12 (9.0)	0.59	0.443
Tuberculosis	0 (0.0)	7 (2.4)	0.52	0.472	0 (0.0)	4 (1.8)	0.27	0.601
Cancer	0 (0.0)	5 (1.7)	0.73	0.393	1 (6.7)	5 (2.2)	1.12	0.290
Seizure	0 (0.0)	4 (1.4)	0.41	0.520	0 (0.0)	4 (1.8)	0.27	0.601

*Psychiatric status was determined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition algorithm as described in the text. PTSD indicates posttraumatic stress disorder. Medical conditions for this study are defined as self -reported history as described in the text

Table 6. PTSD + Depression and asymptomatic respondents*

Comorbid medical conditions	Baseline N=534 (100%)				Endpoint N=376 (70.4%)			
	PTSD + Depression 110 (20.6)	Asymptomatic 294 (55.0)	χ^2	P	PTSD + Depressio 52 (13.8)	Asymptomatic 294 (55.0)	χ^2	P
High blood pressure	61 (55.5)	80 (27.2)	58.02	<0.001	27 (51.9)	49 (22.0)	18.91	<0.001
Heart disease	55 (50.0)	51 (17.3)	18.68	<0.001	27 (51.9)	61 (27.4)	11.70	0.001
Anemia	50 (45.5)	42 (14.8)	36.97	<0.001	35 (67.3)	57 (25.6)	33.01	<0.001
Arthritis	48 (43.6)	48 (16.3)	39.83	<0.001	16 (30.8)	40 (17.9)	4.28	0.039
Kidney disease	32 (29.1)	36 (12.2)	16.22	<0.001	13 (25.0)	32 (14.3)	3.50	0.062
Asthma	27 (24.5)	33 (11.2)	11.23	0.001	16 (30.8)	20 (9.0)	17.62	<0.001
Ulcer	16 (14.7)	29 (9.9)	1.86	0.173	6 (11.8)	8 (3.6)	5.73	0.012
Stroke	16 (14.5)	14 (4.8)	11.15	0.001	5 (9.6)	5 (2.2)	6.54	0.011
Diabetes	14 (12.8)	21 (7.1)	8.03	0.005	4 (7.7)	3 (1.3)	6.85	0.009
Liver cirrhosis	12 (10.9)	14 (4.8)	5.02	0.025	15 (28.8)	10 (4.5)	30.28	<0.001
Gynecological	8 (7.3)	21 (7.1)	0.00	0.564	9 (22.0)	12 (9.0)	5.02	0.025
Tuberculosis	7 (6.4)	7 (2.4)	6.04	0.014	1 (1.9)	4 (1.8)	0.00	0.950
Cancer	4 (3.6)	5 (1.7)	0.48	0.490	0 (0.0)	5 (2.2)	1.19	0.276
Seizure	1 (0.9)	4 (1.4))	0.13	0.715	0 (0.0)	4 (1.8)	0.93	0.335

* Psychiatric status was determined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition algorithm as described in the text. PTSD indicates posttraumatic stress disorder. Medical conditions for this study are defined as self - reported history as described in the text

At baseline half of depressed subjects suffered from high blood pressure (N=53, 53.3%) and heart disease (N=45, 45.5%), and when compared to asymptomatic subjects, the difference reached the level of statistical significance (chi square=22.92, df=1, p<0.001; chi square=31.70, df=1, p<0.001). Furthermore, depression was significantly more associated with eight other medical conditions such as anemia, arthritis, kidney disease, asthma, duodenal or ventricular ulcer, stroke, diabetes and epilepsy. Three years later, depression was still significantly associated with all the above mentioned conditions except stroke (chi square=0.38, df=1, p=0.536) and epilepsy (chi square=0.16, df=1 p=0.694). Data in details are given in Table 4.

Table 5 shows associations between PTSD and medical conditions at baseline and endpoint. Again, at baseline PTSD was statistically significantly more frequently (p<0.05) associated with subjects′ reports of being diagnosed with heart disease, and stroke. At endpoint, subjects suffering from PTSD were more frequently suffering from asthma and liver cirrhosis.

Apart from looking at PTSD and depression separately, we also analyzed subjects who suffered from these two psychiatric disorders at the same time (N baseline=110, 20.6%, N endpoint=52, 13.8%, chi square =6.910, df=1, p=0.009). At baseline, this group was characterized with significantly more cases of heart disease, high blood pressure, arthritis, anemia, kidney disease, asthma, stroke, liver cirrhosis, diabetes and cancer. Three years later subjects reported following comorbid medical conditions - heart disease, high blood pressure. arthritis, asthma, anemia, stroke, liver cirrhosis, duodenal or ventricular ulcer, diabetes and gynecological conditions were more frequently present in this group. Data in details are given in Table 6.

DISCUSSION

In this study we aimed to explore the relationship between psychological and somatic health problems in Bosnian refugees in a three year follow-up study. Our major finding is that medical conditions were more frequent in subjects who suffered from PTSD co-morbid with depression and depression alone, than in subjects who were asymptomatic or suffered only from PTSD.

It has been already reported that people who suffer from PTSD have more medical problems. However, only two studies were performed among civilians. Breslau & Davis et al. (1992) reported that young adults who suffered from PTSD for more than one year, unlike those who suffered from it for a shorter period of time, had more medical conditions. Sareen et al. (2007) examined the prevalence and correlates of PTSD in large population-based study and showed that physical health problems were more prevalent among respondents with PTSD compared to those without PTSD. Significantly more studies were performed among combat veterans. For example Shalev and colleagues (1990) found that veterans more frequently reported cardiovascular, hematological, gastrointestinal, audiological difficulties as well as headaches and lower back pain problems when compared to the control group. Similarly, Wolf and collaborators (1994) found that PTSD is connected to increased likelihood of cardiovascular, gastrointestinal, gynecological, ophthalmological/otolaryngological, dermatological illnesses as well as pain. In another study, Kadojić et al. (1999) showed that a group of displaced persons at the time of study exhibited significantly higher rates of arterial hypertension, hyperlipidemia and obesity than subjects in the control group. Long and coauthors (1992) also

reported that PTSD was associated with increased numbers of both: symptoms and chronic disorders. Interestingly, there are only few studies that looked into this problem from the point of trauma exposure (number of lifetime traumas or traumatic events). For example, Cloitre et al. (2001) examined the relationship between the number of lifetime traumas, PTSD, and physical health among women with history of a childhood abuse. Their results suggested that number of interpersonal traumas was a significant predictor of physical health problems diagnosed by physicians, not the symptoms of PTSD. This study suggested that the cumulative burden of traumas may lead to medical problems independent of PTSD symptomatology. Since refugees are more likely to have experienced a great number of traumas, cumulative trauma may be an important cofounder in the relationship between PTSD and chronic medical conditions as it had been shown in work of Sledjeski et al. (2008).

Our results indicate that in our longitudinal study almost all subjects with PTSD were also suffering from both depression and chronic medical conditions. This is interesting, especially in the relation to the above-mentioned studies because it clearly shows what happens when depression is "added" to the equation. Depression is often chronic medical condition and depressed people usually report more physical complaints and use more medical treatment than non-depressed individuals. Depression is often comorbid with other medical conditions, such as diabetes, hypertension, and arthritis and it often worsens their associated health outcomes (Ciechanowski et al. 2000, Moussavi et al. 2007). Yates and colleagues (2004) in their large depression treatment study have shown that 53% of depressed patients had significant medical comorbidity. In our study, at baseline, 18.5% of our subjects had depression, and approximately half of depressed subjects suffered from high blood pressure and heart disease. Compared to asymptomatic subjects, the difference was statistically significant. Also, depression was significantly more associated with anemia, arthritis, kidney disease, asthma, ulcer, stroke, diabetes and seizure. At the end point 22.8% of subjects had depression, which was still significantly associated with all of the above mentioned conditions except stroke and seizure. Research done on the general population has shown that 60-65% subjects with current major depression also had at least one more psychiatric diagnosis (De Graaf et al. 2002, Rush et al. 2005). Blanchard et al. (1998) examined data from 107 motor-vehicle accident victims and their results indicated that PTSD and major depression were correlated but independent responses to trauma, and that those who suffered from PTSD and depression were more distressed. Depression is a common comorbid condition among individuals with PTSD. Southwick, Yehuda and Giller (1991) found that 53.4% of the Vietnam veterans suffering from PTSD had comorbid major depression. In civilian population, Breslau et al. (1992) in their study of young urban adults who went through various traumas, found that 9.2% had developed PTSD and that 36.6% of those with PTSD met the criteria for major depression. In their research of consequences of PTSD and depression as different disorders, Blanchard at al. (1998) found that the only difference is that those who have more depressive symptoms are more likely to endorse worthlessness and suicidal ideation. Another study by Miranda et al. (2002) supported the hypothesis that depression would mediate the relationship between PTSD and subjective reports of poor physical health. This study examined the role of comorbid depression in somatic complaints of 32 individuals with civilian-based PTSD and found that the relationship between PTSD severity and physical symptom reports was no longer significant if depressive symptoms were included.

Limitations of our study are primarily related to the war and early post-war time in which the study was conducted, so applied study design was only possible to carry through with this, in that period of time, highly vulnerable refugee population. The variables are based on self-reported data: measures of trauma and health status. Physical examinations were not conducted due to the facts explained previously. Secondly, in this study we did not control for cumulative burden of traumas (number of traumatic events) which may also be considered as a limitation.

The accuracy of reporting of trauma events by refugees themselves has been shown in previous reviews (Mollica & Caspi-Yavin 1991, Willis 1998). We did not use structured clinical interviews and it was unclear to what extent the rates of self-reported symptoms for PTSD and depression on HTQ and HCSL-25, respectively, would match clinical diagnosis. HTQ and HCSL-25 have been validated against a clinical criterion standard in other refugee settings (Smith Fawzi et al. 1997, Oruc et al. 2008), supported by cross-validation that links checklist positive diagnosis and disability (Mollica et al. 1999). DSM-IV multidimensional algorithm was also used in the large scale epidemiological study with Kosovo Albanians (Cardozo et al. 2000). Evidence for medical illnesses came from self-reports. Even if those self-reports may not always provide valid information about health status, as they can be strongly influenced by psychological states and processes, they cannot be neglected as completely non-valid, because they can be valid indicators of physical status to some extent. McHorney et al. (1992) and Piljs et al. (1993) have shown that in their work.

CONCLUSIONS

In conclusion, this study of Bosnian refugees performed in three years follow-up reveals a continued high level of psychiatric morbidity, and somatic morbidity connected to them. It is equally important that mental health practitioners, as well as general practitioners, recognize this problem. The general practitioners are usually the first ones in touch with traumatized persons.

It is important for them to monitor medical complaints and consider the possibility that their patients' physical status might be related to psychical one. With that approach we can avoid, a paradigm of mind-body dualism that is still influential in our practice of health services delivery, and give opportunity for better detection and treatment of PTSD and/or depression co-morbidity related to medical conditions of traumatized persons.

Acknowledgements:

Source(s) of research support: This study was supported by grant MH57806-02 from the National Instiute of Mental Health, Bethesda, Md.
We are thankful to all participants for sharing their most intimate experiences with us. We acknowledge interviewers, many themselves at that time refugees, who made the data collection possible.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 450-458 *Original paper*

STRESS, DEPRESSION AND BURNOUT AMONG HOSPITAL PHYSICIANS IN RIJEKA, CROATIA

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SUMMARY

Background: *Six years of recent ongoing economic and structural crisis in Croatia have brought to a significant decrease of socioeconomic standard in our country, and had an important impact on the health care system. In this background we examined the prevalence of depression and burnout and their association with work stressors.*

Subjects and methods*: Cross sectional survey was conducted with self reported questionnaires in 459 hospital physicians in Rijeka, Croatia. Physicians were divided into three groups: surgical, nonsurgical and diagnostic group. Socio-demographic and work-related characteristics questionnaire, Occupational Stress Assessment Questionnaire (OSAQ), Maslach Burnout Inventory-Human Services Survey (MBI-HSS) and Beck Depression Inventory II (BDI-II) were used. Sperman correlation and logistic regression were calculated to rank association between stressors at work with depression and burnout syndrome.*

Results: *Response rate was 62.3%, (286/459). Every fifth doctor experienced all examined stressors in the workplace as stressful. The prevalence of moderate and severe depression was 12.2%. High levels of emotional exhaustion were 43.6%, depersonalization 33.5%, and lack of personal accomplishment 49.1%. There was no statistical difference in surgical, nonsurgical and diagnostic groups in depression and all domains of MBI-HSS. Almost all stressors were correlated with depression and burnout syndrome. Most of the perceived stressors were significant predictors of burnout syndrome and depression.*

Conclusions: *High levels of burnout domain compared to overall results from similar studies from other countries, placed the results in our sample on the higher end of the range, while results for depression after adjustment with lower cutoff point would be similar to those usually found in research literature. Our study showed that burnout is highly prevalent among Croatian physicians. Target interventions at the workplace should be considered as one of the strategies to reduce negative impact of work stress on physicians' mental health.*

Key words: *burnout – depression – physicians – hospital - stress*

* * * * *

INTRODUCTION

The prevalence of some mental diseases and mental health problems in physicians are higher than in general population (Wall et al. 1997, Tyssen 2007), although, given their overall socioeconomic status and educational level, otherwise should be expected.

The most frequent disorders among physicians are alcohol use disorders, prescription drug use (minor opiates and benzodiazepine tranquilizers) (Hughes et al. 1992) and depression (Unrath et al. 2012) with the significantly higher suicide rate (Schernhammer & Colditz 2004). Even if physicians recognize symptoms of mental disorder, they often do not seek professional help and continue with their professional activity. They usually deny existence of problems (Stanton & Randal 2011) because asking for help could be interpreted by their colleagues and patients as a professional weakness and working disability.

Medical profession is generally perceived as a very stressful occupation. Although some stressors in health care settings are inevitable and invariable, such as dealing with incurable patients and their dying, there are some variable workplace stressors that represent a risk for medical professionals: work organization, financial issues, administration, interference with family and social life, relationships with colleagues and patients, and work demand (long working hours, workload, and pressure) (Firth-Cozens 1998, Knezevic 2010, Michie & Williams 2003, Rout et al. 1989). Some of the work-stress factors are associated with burnout syndrome (Selmanovic et al. 2011), depression symptoms (Tomioka et al. 2011) and a poorer quality of mental health generally (Michie & Williams 2003).

Occupational stress has a negative impact on physician's work performance as well, reducing the quality of patient care (Firth-Cozens 2001), and influencing sickness absence (Michie & Williams 2003) and decision to leave a profession (Chonh et al. 2004). The above mentioned groups of variable factors seem to be especially meaningful to investigate, because they have an important effect on work related health and mental health specifically. Once closely defined, these variable factors could be possibly modified and their impact on the mental health of medical professionals reduced.

Depression as well as burnout syndrome represents some of the mental health problems in physicians and a potential risk for the lower work performance (Fahrenkopf et al. 2008, Shanafelt et al. 2010).

Burnout syndrome is a work related state dominantly characterized by dysphoric symptoms, with emotional exhaustion as its core feature (Schaufeli & Buuk 2003). It is considered to be a prolonged response to chronic emotional and interpersonal job related stressors. The concept of burnout syndrome consists of three domains: emotional exhaustion (EE), depersonalization (DE) and lack of personal accomplishment (PA) (Maslach et al. 2001). Although research results are not consistent, burnout syndrome is more common in physicians than general working population (Shanafelt et al. 2012). The incidence of burnout and depression in physicians, as well as their relation to physicians' perception of exposure to various forms of work stress were assessed in numerous studies (Chonh et al 2004, Selmanovic et al. 2011, Shanafelt et al. 2012, Tomioka et al. 2011). Health care system in Croatia is financed through social medical insurance paid by citizens and budget revenues. During the last 25 years Croatia underwent the process of political transition, with profound social and economic changes, including 4-year war. Six years of recent ongoing economic and structural crisis has brought to a significant decrease of socioeconomic standard in our country, and had an important impact on the health care system. On the other hand, new technologies and population aging that happened simultaneously with global changes in the workfield present further challenges that Croatian physicians have to cope with. Besides this, physicians in Croatia are facing numerous everyday problems: staff shortage resulting in excessive workload, shortage of material supplies, inadequately designed working spaces, and inappropriate and aged equipment.

Several studies conducted in Croatia and neighboring countries measured the prevalence of burnout and work stress in physicians working in different clinical contexts (Cubrilo-Turek et al. 2006, Gregov et al. 2011, Pejuskovic et al. 2011) but to our knowledge there was no research on association between different work stressors with depression and burnout syndrome in hospital physicians. Also, numerous studies from culturally and socio-economically more or less different countries were published, measuring the work stress and prevalence of burnout and depression in physicians in different medical specialties, and evaluating the intercorrelations of these phenomena (Gallery et al. 1992, de Oliveira et al. 2013, Visser et al. 2003). Having above mentioned contextual differences in mind, we were interested in conducting such research in transitional country, such as Croatia certainly is.

The aim of this study was to determine the prevalence of burnout and depression. Given the considerably different working and socioeconomic context, we expected that burnout and depression in Croatian hospital physicians would be more prevalent than in their western counterparts with higher prevalence of burnout in the surgical group. There are also differences in perception of the work related stressor. We expected that organization of work and financial issues were work related stressors that are perceived as the most stressful. According to the literature, stressors at work are a significant predictor of depression and burnout syndrome.

SUBJECTS AND METHODS

Participants and study design

This cross sectional study was carried out during 2013. The target populations were all physicians working at Clinical Hospital Center Rijeka placed at three locations (site Rijeka, site Kantrida, site Sušak). The response rate was 286/459 (62.3%). Among 286 participants there were 218 specialists, 64 residents and there was no data for four participants.

Physicians were divided into three groups based on the type of the work and potentially similar stressors: 1. surgical group - physicians who work in operating rooms, emergency rooms or departments with surgical activity (surgery, gynecology, anesthesiology, otorhinolaryngology, ophthalmology, and emergency medicine), 2. nonsurgical group - physicians who work in the nonsurgical departments (pediatrics, oncology, internal medicine, neurology, physical medicine and rehabilitation, infectology, psychiatry, dermatology and transfusiology), 3. diagnostic groups - physicians who work in the diagnostic departments (radiology, microbiology, pathology and cytology).

The examinees were approached in person at their workplace or via the head of department. Ethical approves for this research were gained from the Ethical Committee of Medical Faculty Rijeka and Ethical Committee of Clinical Hospital Center Rijeka.

Questionnaires

Four self-administrated questionnaires were used in this survey: Socio-demographic and work-related characteristics questionnaire, Occupational Stress Assessment Questionnaire (OSAQ), Beck Depression Inventory II (BDI-II) and Maslach Burnout Inventory-Human Services Survey (MBI-HSS).

Socio-demographic (gender, age, and marital status items) and work-related characteristics questionnaire (group of specialization, length of service, consideration about leaving the job, work private life interference items) were designed for this survey. Stress at work was measured using Occupational Stress Assessment Questionnaire (OSAQ) especially designed for health care workers. A questionnaire was developed (piloted and validated) by the Department for Environmental Health Andrija Stampar School of Public Health, Zagreb, Croatia (Milosevic 2009).

The questionnaire consists of six domains: F1 domain - Organization of work and financial issues (10 items: inadequate income, inadequate assets for work, inadequate working space, little opportunity for professional progress, scarce communication with superiors, insufficient number of employees, poor organization of work,

everyday unpredictable situation, administrative work, overload); F2 domain - Public criticism (7 items: threat of lawsuits, inadequate expectations by patients and families, inappropriate public criticism, misinformed patients by the media and other sources, conflicts with the patient and family members, inability to separate professional and private life, 24 hours responsibility); F3 - Hazards at the workplace (6 items: fear of exposure to ionizing radiation, fear of exposure to inhaled anesthetics, fear of exposure to cytostatic, fear of infections, fear of injury with a sharp object, dealing with incurable patients); F4 - Interpersonal conflicts at the workplace (4 items: conflicts with colleagues, conflicts with superiors, conflicts with other co-workers, scarce communication with colleagues); F5 - Shift work (4 items: 24-hours shifts, night work, overtime, shift work); F6 - Professional and intellectual demands (6 items- introduction of the new technology, adoption of new information from the profession, lack of appropriate continuing education, lack of literature, time deadlines for the tasks, limited time for patients). Each item is ranked as a self-perceived work related stress from 1 (not stressful at all) to 5 (extremely stressful). Each domain, as well as total stress, has a score in range from 0-100. The domain is perceived as stressful if the score is above 60. Depression was measured using Beck Depression Inventory II (BDI-II). It consists of 21 items, each item describing one of the symptoms of self-reported depression. The items are scored from 0-3 depending on the severity of depression. The total score ranges from 0-63. For classification of the severity of depression the standardization made on Croatian population was used: 0-11 minimal, 12-19 mild, 20-27 moderate and 28-63 severe depression (Beck 2011). Burnout syndrome was measured using Maslach Burnout Inventory – Human Services Survey (MBI-HSS). MBI-HSS consists of three domains: emotional exhaustion (EE) (9 items), depersonalization (DE) (5 items) and personal accomplishment (PA) (8 items). Each item is ranked on a seven point Likert scale from 0 (never) to 6 (each day). The scores of each domain are summed and divided in three levels: low, average and high level of burnout. The categorization of the levels was defined based on recommendations made for Croatian medical professionals: EE (low ≤18, average 19-26, high ≥27), DE (low ≤5, average 6-9, high≥10) OP (low ≥40, average 34-39, high≤33) (Maslach 2012).

Statistics

Descriptive analyses were used for calculation means, standard deviation and proportion for continuous and categorical variables. For group comparison we used Kruskal-Wallis, Chi square tests and one way ANOVA. The correlation was calculated using Spearman rho correlation coefficient. Logistic regression was used to identify predictors of burnout and depression. The level of statistical significance was set as α=0.05. All results were processed by STATISTICA version 10 (Stat soft, Tulsa, USA).

RESULTS

Participants socio demographic and job characteristics

Of the 459 participants, 286 returned questionnaires (response rate 62.3%). Socio-demographic characteristics of the sample were; gender: female 164 (58.4%) and male 117 (41.6%), age: 45.9±10.6 (mean±SD), marital status: single 52 (18.4%), married 191 (68%), cohabiting 12 (4.3%), divorced 23 (8.2%) and widowed 3 (1.1%). Work-related characteristics were; average work experience: 18.9±10.9 years (mean±SD), consideration about leaving the workplace: never 73 (26.1%), sometimes 126 (45%), often 57 (20.4%), constantly 13 (4.6%) and already taking actions to change actual workplace 11 (3.9%). Work-private life interference, examinees stated that their job has negative effect on their private life: never 12 (4.5%), sometimes 88 (33.2%), often 111 (41.9%) and all the time 54 (20.4%).

Association of socio-demographic characteristics, stressors at work with depression and burnout syndrome

Socio-demographic characteristics of examinees, stressors at work, depression and burnout scores according to the specialization group are shown in Table 1.

We found gender distribution in those three groups significantly different (χ^2=25.86, df=2, P<0.001,) with the highest percent of women in diagnostic group (85.2%), then in non-surgical group (66.7%) and the lowest in the surgical group (40.9%). There was no significant difference in age between these three groups.

The most stressful factor at work in all three groups were F1 - Organization of work and financial issues (44.0%) followed by F5 - Shift work (43.3%). One third to almost one half of the respondents in each specialization group perceived those domains as stressful. F3 - Hazards at the workplace domain differs surgical group significantly from the other two groups (χ^2=17.72, df=2, P<0.001) and there was no significant difference between groups in other stressors' domains.

The prevalence of moderate and severe depression was 9.9% in the surgical group, 11.1% in diagnostic group and 14.2% in non-surgical group, total was 12.2%. We have not found a significant difference between groups.

Results of MBI-HSS showed that EE is the most frequent in high level range in all three specialization groups (surgical group 40.4%, nonsurgical group 46.9%, and diagnostic group 38.5%). The total prevalence of high level range of EE was (43.6%).

The surgical group has very similar results in high and low level range (40.4% towards 41.3%). The highest rate of DE is in the low level range in all three specialization group (surgical group 47.7%, nonsurgical group 49.3%, and diagnostic group 69.2%). The total

Table 1. Socio-demographic characteristics, stressors at work, depression and burnout scores according to the specialization groups

	Surgical group n/N (%)	Nonsurgical group n/N (%)	Diagnostic group n/N (%)	Total n/N (%)	P
Gender					
female	45/110(40.9)	96/144(66.7)	23/27(85.2)	164/281(58.4)	<0.001
male	65/110(59.1)	48/144(33.3)	4/27(14.8)	117/281(41.6)	
Age (mean + SD)	47±11.5	47±10.07	43±9.7	45.9±10.6	0.433
F1 Organization of work and financial issues/ perceived as stressful	48/106(45.3)	65/144(45.1)	9/27(33.3)	122/277(44.0)	0.526
F2 Public criticism/ perceived as stressful	42/108(38.9)	61/146(41.8)	5/26(19.2)	108/280(38.6)	0.091
F3 Hazards at the workplace/ perceived as stressful	10 /94(10.6)	0/135 (0.0)	0/25(0.0)	10/254(3.9)	<0.001
F4 Interpersonal conflicts at the workplace/ perceived as stressful	19/93(20.4)	27/139(19.4)	3/27(11.1)	49/259(18.9)	0.562
F5 Shift work/ perceived as stressful	37/84(44.0)	57/126(45.2)	7/23(30.4)	101/233(43.3)	0.429
F6 Professional and intellectual demands/ perceived as stressful	9/92(9.8)	8/133(6.0)	0/25(0.0)	17/250(6.8)	0.203
F total/ perceived as stressful	17/81(21.0)	24/119(20.2)	2/22(9.1)	43/222(19.4)	0.461
BDI-II					
minimal or mild	100/111 (90.1)	127/148 (85.8)	24/27(88.9)	251/286(87.8)	0.600
moderate or severe	11/111(9.9)	21/148(14.2)	3/27(11.1)	35/286(12.2)	
EE					
low*	45/109(41.3)	38/147(25.9)	9/26(34.6)	92/282(32.6)	
average*	20/109(18.3)	40/147(27.2)	7/26(26.9)	67/282(23.8)	0.110
high*	44/109(40.4)	69/147(46.9)	10/26(38.5)	123/282(43.6)	
DE					
low*	52/109(47.7)	72/146(49.3)	18/26(69.2)	142/281(50.5)	
average*	16/109(14.7)	25/146(17.1)	4/26(15.4)	45/281(16.0)	0.256
high*	41/109(37.6)	49/146(33.6)	4/26(15.4)	94/281(33.5)	
PA					
low*	27/109(24.8)	28/146(19.2)	4/26(15.4)	59//281(21.0)	
average*	36/109(33.0)	43/146(29.5)	5/26(19.2)	84/281(29.9)	0.259
high*	46/109(42.2)	75/146(51.3)	17/26(65.4)	138/281(49.1)	

*low, average and high refers to the level of burnout in particular dimension, not to the score on the scale

prevalence of DE was the most frequent in low range (50.5%). PA is the most frequent in the highest level range in all three specialization group (surgical group 42.2%, nonsurgical group 51.3%, and diagnostic group 65.4%). The total prevalence of PA was the most frequent in high range (49.1%). We have not found a significant difference in any of domains of MBI-HSS between these three groups.

Correlations between stressors at work and depression as well as stressors at work and burnout syndrome are shown in Table 2. Beside F3 - Hazards at workplace and PA domain, all correlations were statistically significant. Depression has the strongest correlation with F6 - Professional and intellectual demands (0.37). Domain of EE has the strongest correlation with F1 Organization of work and financial issues (0.51), DE with F5 - Shift work (0.36) and PA with F1 - Organization of work and financial issues (-0.22) (lower score on PA scale indicate the severity of the problem). Regarding total stress score, the strongest association was found with EE domain (0.58).

Results of logistic regression for assessing predictors of depression and burnout are shown in Table 3. Professional and intellectual demands had the strongest effect on depression (OR 1.06). All of the examined stressors were predictors of depression except F3 - Hazards at the workplace. EI domain has the strongest association with all stressors at work, value of OR is the highest compared to other domains. Organization of work and financial issue was the strongest predictor of EI domain.

Depersonalization was predicted almost similarly with all stressors except except F3 - Hazards at the workplace, it showed similar results as for depression. Organization of work and financial issue and shift work were significant predictors of a personal accomplishment domain. Age can be interpreted as a protective factor for personal accomplishment (OR 0.96).

Table 2. Correlations between stressors at work, depression and burnout syndrome

Stressors at work	BDI-II Spearman rho (p value)	MBI-HSS EE Spearman rho (p value)	MBI-HSS DE Spearman rho (p value)	MBI-HSS PA Spearman rho (p value)
F1 Organization of work and financial issues	0.33 (<0.001)	0.51 (<0.001)	0.30 (<0.001)	-0.22 (<0.001)
F2 Public criticism	0.32 (<0.001)	0.38 (<0.001)	0.31 (<0.001)	-0.14 (0.024)
F3 Hazards at the workplace	0.19 (0.002)	0.28 (<0.001)	0.17 (0.006)	-0.02 (0.792)
F4 Interpersonal conflicts at the workplace	0.36 (<0.001)	0.40 (<0.001)	0.33 (<0.001)	-0.17 (0.006)
F5 Shift work	0.31 (<0.001)	0.38 (<0.001)	0.36 (<0.001)	-0.19 (0.005)
F6 Professional and intellectual demands	0.37 (<0.001)	0.45 (<0.001)	0.32 (<0.001)	-0.18 (0.004)
Total F1-F6	0.43 (<0.001)	0.58 (<0.001)	0.42 (<0.001)	-0.23 (<0.001)

Table 3. Predictors of depression and burnout - logistic regression results

Predictor	BDI-II Moderate or severe depression		MBI-HSS EE		MBI-HSS DE		MBI-HSS PA	
	OR	95%Cl	OR	95%Cl	OR	95%Cl	OR	95%Cl
Age	1.02	0.98-1.05	1.00	0.98-1.01	0.98	0.96-1,01	0.96	0.94-0.99
Gender	0.67	0.31-1.44	0.83	0.51-1.35	1.10	0.67-1.83	0.66	0.41-1.07
F1 Org. of work and financial issues score	1.04	1.02-1.06	1.06	1.04-1.07	1.03	1.02-1.05	1.02	1.01-1.04
F2 Public criticism score	1.03	1.01-1.05	1.03	1.02-1.05	1.03	1.01-1.04	1.01	0.99-1.02
F3 Hazards at the workplace score	1.00	0.99-1.03	1.03	1.01-1.04	1.01	0.99-1.03	1.00	0.99-1.02
F4 Interpersonal conflicts at the work score	1.03	1.01-1.05	1.02	1.02-1.04	1.02	1,01-1.03	1.00	0.99-1.02
F5 Shift work score	1.02	1.01-1.03	1.02	1.01-1.03	1.02	1.01-1.03	1.01	1.01-1.02
F6 Professional and intellectual demands score	1.06	1.03-1.09	1.05	1.03-1.07	1.03	1.01-1.05	1.02	0.99-1.03
Total F1-F6	1.06	1.03-1.09	1.08	1.06-1.11	1.05	1.03-1.07	1.03	1.01-1.04

DISCUSSION

Summary of main findings

In the study performed on a sample of Croatian hospital, there were no significant differences in the perceived work stress and frequency of burnout and depression among surgical, non-surgical and diagnostic group. Every fifth doctor experienced all examined stressors in the workplace as stress with large differences within each group of stressors. The most common stressors were the organization of work, financial issues and shift work. The prevalence of moderate and severe depression was 12.2%. High level of EE was 43.6%, DE 33.5%, and lack of PA 49.1%. Almost all stressors are correlated with depression and burnout syndrome. Most of the perceived stressors were significant predictors of burnout syndrome and depression.

Comparison of results

In the existing literature there are considerable differences regarding the conceptualization of the components/dimensions of the work stress and the methodology of its measurement. Although these differences make comparison between our data and previous research somewhat difficult, nevertheless we made some qualitative comparison.

As we previously mentioned, we conveniently divided our sample in three clusters, taking into account different working conditions and therefore work stressors in the three categories. We analyzed potential differences between these groups. Such division into three clusters was made partly considering common working conditions, and partly considering the relatively small sample size in most medical specialties, which made comparisons between specialties impossible.

F1 - Organization of work and financial issues and F5 - Shift work were the work stressors perceived as most important by the participants of our study.

Working context of doctors in Croatia appears to be different with relatively low wages and far lower socio-economic standard, with substantial physician shortage in addition. We felt it was reasonable to expect some differences in the perceived importance of various stressors.

In the research literature on work stress in health workers, shift work (24 hours duty, night shifts, overtime work) seems to be the source of stress that is regularly punctuated. Shift works stressors appear to be irrespective of socioeconomic context, and it could be regarded as the typical stressor for medical profession (O'Sullivan et al. 2005, Turk et al. 2014). Although, generally, various work stresses in physicians are investigated, we made a selection of work stresses commonly perceived as most prominent in health workers in our country. Contrary to our expectation there were no significant differences between three specialty groups (with exception of F3 - Hazards at workplace domain in surgical group).

In the research conducted on hospital physicians in Zagreb, (Croatia) (Knezevic 2010) and Tuzla (Bosnia and Herzegovina) (Selmanovic et al. 2011) work organization and finances were identified as the most important work stressors. In the studies from developed countries finances represent considerably less punctuated source of work stress, with doctor-patient relationship, impact of work on private life, control over practice environment, job demands and social support being the most prominent identified stressors (Campolieti et al. 2007, Freeborn 2001, Visser et al. 2003).

The prevalence of moderate and severe depression in our sample was 12.2%, with similar results in all three specialty groups (9.9-14.2%). Compared to the range of prevalence of depression in hospital physicians from different studies measured with self-reported questionnaires (19-29%) (Embriaco et al. 2012, Erdur et al. 2006, Gallery et al. 1992, Ruitenburg et al. 2012), the prevalence of depression in our sample is relatively lower, although it should be noted that in most studies depression is defined with total score of 17 (Erdur et al. 2006) as a cut off point for BDI-II, and in our study we used total score of 20 as a cut off point for severe and moderate depression.

The BDI specificity was higher in our research, so this should be interpreted as an evident source of lower prevalence of depression in our sample, although examples of studies with similar results regarding the prevalence of depression could be found (prevalence of 11.3% for moderate and severe depression in physicians in Michigan) (Schwenk et al. 2008). If our results would be adjusted to include definition of depression with lower cut off point, they would be similar to those usually found in research literature.

In our study we have evaluated the prevalence of burnout syndrome in a sample of hospital physicians using the MBI-HSS. As we previously discussed, given the observable differences in the socioeconomic and working context between Croatian hospital physicians compared with doctors working in western developed countries, we expected that the prevalence of burnout in our sample would be at least moderately higher compared to samples from developed countries. Extensive research of literature on the subject, shows that the prevalence of high scores on each domain of MBI-HSS among hospital physicians in developed countries varies between 13-53% for EE, 13-61% for DE, and 4-50% for PA, with a remarkable tendency toward moderate or lower end of the mentioned ranges (Campbell et al. 2001, Graham et al. 1996, Grunfeld et al. 2000, Lloyd et al. 1994, Selmanovic et al. 2011, Shanafelt et al. 2009). Results from our study indicate that 34-49% of the participants had one high result on at least one MBI-HSS subscale domain which, compared to overall results from similar studies from other countries, placed the results in our sample on the higher end of the mentioned range.

According to the results, although the large share of the participants in our study describe themselves as emotionally exhausted, with a pronounced feeling of lack of personal accomplishment, they still manage not be cynical towards their patients, as could be expected from the overall results.

We found one study eligible for comparison, simply on the ground of assumption that we share similar socioeconomic and cultural context. A study was conducted in Tuzla, Bosnia and Herzegovina few years ago, where in hospital doctors high level of EE in 37.4%, a high level of DE in 45.6%, and a low level in perceptions of PA in 50.3% were established, which makes the overall prevalence of burnout in this study comparable to our data (Selmanovic et al. 2011).

Research conducted on a sample of primary care physicians in Croatia (2012), compared to our sample of hospital physicians, showed a considerable difference in the proportion of high levels in the domains of DE and lack of PA (16% and 15.2%, respectively), with almost similar results in the domain of EE (42.2%) (Ozvacic et al. 2013). These data possibly indicate higher prevalence of burnout among hospital physicians in Croatia which could be interpreted as an indication of considerably poorer working conditions, although further research is needed to allow such conclusion.

Contrary to our expectations based on their different working contexts, in our sample there were no statistically significant differences in the prevalence of self-perceived burnout between surgical, non-surgical and diagnostic specialty groups. Two other comparative studies also didn't show any significant difference in burnout prevalence across different specializations (Aldrees et al. 2013, Martini et al. 2004).

Relatively high prevalence of burnout in our sample, combined with specific socioeconomic and working context, could offer explanations for the relatively high proportion of physicians in our research (28,2%) who were frequently considering to leave the current working position. Also negative effect of work on private life were perceived often and all the time in 62.3% of participants.

It is noteworthy but regularly omitted from discussions in scientific papers on depression in physicians, that given the primary selection, higher socioeconomic status and higher education, the considerably lower prevalence of depressive disorders in physician population should be expected. Also, because of generally higher brain and cognitive reserve in physician population, one could hypothesize that work stress would lead to burnout and clinical depression with considerable delay and with less severe functional consequences.

As previously mentioned the relationship between work stressors, depresion and burnout is complex. Our study indicates the association between stressors at work with depression and burnout syndrome. The correlation between most of the work stressors measured in our study with depression (0.31-0.37), and with certain burnout domains DE (0.30-0.33) were in a similar range, with weak and negative correlation with PA (-0.14-0.22) (except F3 Hazards at workplace). EE is the domain which showed the strongest correlation with stressors at work in our study. EE is generally regarded as the basic individual stress component of the syndrome (Maslach et al. 2001). For example, longitudinal research of McManus et al. confirmed that emotional exhaustion makes doctors more stressed and reversely, stress makes doctors emotionally exhausted (McManus et al. 2002). In line with these finding Biaggi et al. found correlation between stressors at work with emotional exhaustion and aversion to client (Biaggi et al. 2003). Other studies also showed a correlation between stressors at work and burnout (Eckleberry-Hunt et al. 2009, McManus 2004 et al.).

Our study implicated that exposure to professional stress was a predictor of depression and burnout, especially for EE and DE domains. Odds ratio had similar value in range OR 1.01-1.08 for all statistically significant stressor. In other studies are found similar stressors that predict burnout and depression. One of the strongest predictors of burnout was found to be control over schedule and work hours while physician gender, age, and specialty were not strong independent predictors (Keeton et al. 2007). According to another study, job characteristic, especially overload were significant predictors of burnout (Ramirez et al. 1995). A study conducted in physicians from different health care institution found that working shifts were also a significant predictor of all burnout dimensions (Ozyurt et al. 2006). Numerous of studies found that depression is predicted by work stressors like working hours, conflict with a colleague and other physicians (de Oliveira 2013, Embriaco et al. 2012).

The major limitations of this study were cross sectional designs of the study, self reported questionnaires, small response rate (62.3%), and local character of research (only one hospital was included in this research).

CONCLUSION

Depression and burnout are one of major mental health problem among physicians today. Our findings are consistent with other research that emphasizes the importance of stressors at the workplace as a relevant source of specific outcomes that can have a negative impact on health and work quality. Our study showed that burnout is highly prevalent among Croatian physicians. Target interventions at the workplace should be considered one of the strategies to reduce negative impact of work stress on physicians' mental health.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 459-465 *Original paper*

CHARACTERISTICS OF SELF-MEDICATION FOR PAIN RELIEF AMONG FIRST-YEAR HEALTH CARE STUDENTS IN ZAGREB, CROATIA

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SUMMARY

Background: *Taking over the responsibility for one's own health and active participation in eliminating the existing health problems is ever more widespread in the world. Self-medication in the form of using any kind of therapy without previous consultation with medical professionals has been ever more common among student populations in many countries. The aim of this study was to determine the attitudes about self-medication for pain relief and features of self-medication in first-year students of the University of Applied Health Studies in Zagreb.*

Subjects and methods: *The study was conducted using an anonymous questionnaire, which was completed by 389 respondents.*

Results: *Taking painkillers in the past year was reported by 74.6% of respondents, significantly more by female students (80.8%); 62.6% of female students used painkillers once a month versus 45.7% of male students taking analgesics once a year. Ibuprofen was preferred by female students and acetylsalicylic acid by male students. Headache was the most common indication for taking painkillers (76.6%), followed by menstrual discomforts in female students (66.2%) and toothache (28.6%). Significant sex differences were recorded in the choice of drugs, indications for self-medication, and frequency of drug use. There were no differences between study courses.*

Conclusions: *Appropriate student education and improved information transfer between professionals and students are the key elements to ensure judicious, quality and knowledge based use of drugs among students.*

Key words: *self-medication for pain relief – painkillers - health care students - Croatia*

* * * * *

INTRODUCTION

Taking over the responsibility for one's own health and eliminating the existing health problems has been ever more widespread all over the world. The occurrence of pain is one of the symptoms associated with some health problems. The International Association for the Study of Pain describes pain as an unpleasant emotional and sensorial experience associated with a real or potential tissue damage (IASP 1994). Epidemiological studies have shown that even one-third of the population in industrialized countries suffer chronic pain, which poses a huge health, economic and social problem. In the USA, total annual health care costs for pain management in 2010 amounted to 560-635 billion $, including medical cost of pain treatment and economic cost related to sick-leaves, reduced wages and lower productivity (IOM 2011). The objective of pain elimination is to enable normal functioning of the individual in his/her working and daily activities. There are many ways to treat and alleviate pain, with variable efficacy. Some persons tend to reduce pain by physical exercise, use of dressings, rest or other non-pharmacological methods of pain management. Relaxation and distraction can occasionally offer some relief. Yet, pain is most frequently removed by taking painkillers. Pain may occur suddenly, as a distraction, frequently in the situations requiring concentration and engagement from the person. Therefore, there is the need to eliminate pain quickly, mostly on one's own decision, taking pharmacological agents for pain relief without consulting a physician or pharmacist. Self-medication for pain relief is taking painkillers on one's own, without previous consultation with a physician or pharmacist about the type of analgesic to be used and the intensity and localization of pain to be relieved. The reasons for self-medication are numerous and multifaceted. Self-medication is perceived as advantageous for saving time (making appointment, waiting for examination at doctor's office), avoiding payment for examination, and availability of pharmacies everywhere on daily routine. Studies have demonstrated that self-medication is influenced by factors such as age, sex, family, income, society, level of education, previous medical knowledge, previous experience with the same or similar discomforts, attitude about one's own health, satisfaction with and perception of one's own health (Aljinović-Vučić et al. 2005, Figueiras et al. 2000). High education level and professional status also are predictive factors for self-medication (Martins et al. 2002). As expected, scientific research has revealed that self-medication is more common in health care professionals than in the general population (Aljinović-Vučić et al. 2005), probably

because they feel safer when turning to self-medication due to their sharing a great body of health information on a daily basis and attending health care courses during education. Analgesics and antibiotics are the groups of drugs that are most frequently used for self-medication (Hughes et al. 2001). Non-opioid analgesics that are most commonly used as painkillers in Croatia are available as over-the-counter (OTC) drugs; some of them are found on the Croatian Institute of Health Insurance Supplementary List of Drugs but still are the drugs of choice for pain relief in the population. The present study also included spasmolytics as a group of drugs relaxing intestinal smooth muscles and alleviating spasms and accompanying pain. These agents are used for spasm and pain in the gastrointestinal tract, biliary system, urogenital system, and for spastic states in gynecology (inflammation, dysmenorrhea).

Taking drugs for self-medication has been increasingly recorded in the student population worldwide (Burak & Damico 2000, Sawalha 2008). It is quite understandable in the light of the World Health Organization (WHO) promotion of self treatment and assuming responsibility for one's own health. In addition, there is an increasing influence of media on the information and modes of treatment of particular discomforts. Internet has become the main source of health information for many individuals, offering promising solutions in the domain of self-medication. Headache, cold and dysmenorrhea are most frequently mentioned as health problems for which students turn to self-medication. The main reasons for which students opt for self-medication to relieve some health problems include previous experience and mild pain (Gutema et al. 2011). Yet, students are a vulnerable group because they are still in the process of setting their opinion about health issues, while their attitudes about self-medication are influenced by numerous factors. Parental impact is being gradually fading away, while the individual starts making his/her own decisions on health and its protection, along with various impacts exerted by the society, media, Internet and medical courses. All this suggests that student population differs from adult population in their attitudes about self-medication.

The aim of the study was to assess the attitudes about self-medication for pain relief and characteristics of self-medication in first-year students of the University of Applied Health Studies in Zagreb, Croatia.

SUBJECTS AND METHODS

A questionnaire, consisted of three separate parts contained questions which was used to collect data on the leading health problems for which painkillers were used: which drugs were most commonly used and how frequently; the level of students' knowledge about drug side effects and whether they read drug package inserts at all; and use of methods for pain relief other than medication.

The study conducted at the University of Applied Health Studies in April and May 2013 included full-time first-year students attending 6 different studies: Nursing; Physiotherapy; Medical Laboratory Diagnosis; Radiologic Technology; Occupational Therapy; and Sanitary Engineering. Students were asked to complete the survey 15 minutes before or after the course of a certain study. A main researcher explained in detail the objectives and purpose of the research, the concept of the questionnaire and instructions were given. Data on all study subjects were collected by anonymous questionnaire on a voluntary basis. The questionnaire contained questions providing information on socio-demographic characteristics (age, sex, study course); general health of the respondents; characteristics of and attitudes about self-medication (taking painkillers or not; if yes, which drugs and how frequently, for what health problems; the intensity of pain for which analgesic is used; using other methods for pain relief). The study was approved by the University of Applied Health Studies Ethics Committee.

Statistical analysis

The Statistica version 10 (StatSoft Inc., Tulsa, OK, USA) software was used for data entry and analysis. The following statistical methods were employed: descriptive analysis, χ^2-test or Fisher exact test, and t-test. Statistically significant differences were expressed at the 95% level of confidence (p=0.05).

RESULTS

The study sample included 389 students, 297 /76.3%) female and 92 (23.7%) male. Student distribution according to study course and sex is shown in Table 1.

Table 1. Distribution of the University of Applied Health Studies students according to sex and study course

	Female	Male	Total per study course
Study course			
Physiotherapy	63	39	102
Nursing	73	10	83
Occupational Therapy	36	5	41
Radiologic Technology	35	26	61
Medical Laboratory Diagnosis	52	8	60
Sanitary Engineering	38	4	42
Total per sex	297	92	389

As many as 290 (74.6%) subjects reported taking analgesics in the past year, whereas 99 (25.4%) did not. Taking painkillers in the past year was reported by a significantly greater number of female (80.8%) than male (54.3%) students (Pearson's χ^2=25.91; df=1; p<0.0001).

Study subjects were asked to perform a subjective self-assessment of pain on a 1-7 scale, where 1 denotes mild pain and 7 very intense pain. The subjects marked the intensity of the pain they tried to alleviate by drugs. A statistically significant difference was found in pain intensity self-assessment between the groups of subjects having and those not having taken painkillers in the past year. The students having used painkillers in the past year (n=290) reported taking these agents for the mean pain intensity of 5.44 on the scale, whereas those not having taken these agents (n=99) considered it necessary for the mean pain intensity of 6.23 (t-test=-5.42; df=387; between-group difference -0.791; 95%CI -1 to -0.5).

Out of 290 students having used painkillers in the past year, 53.7% reported taking these agents once a month. There was no significant difference in the frequency of using painkillers according to study courses. However, the frequency of using painkillers yielded a statistically significant sex difference (Pearson's χ^2=64.817; df=4; p<0.0001). More than half of female students (n=186; 62.60%) reported taking painkillers once a month and 80 (26.6%) once a year. In contrast, 42 (45.7%) and 23 (25.0%) male students reported taking painkillers once a year and once a month, respectively, whereas 24 (26.1%) male students did not use them at all (Table 2).

Table 2. Frequency of analgesic self-medication according to sex

	Female n (%)	Male n (%)
Never	12 (4.0)	24 (26.1)
1/year	80 (26.9)	42 (45.7)
1/month	186 (62.6)	23 (25.0)
1/week	16 (5.4)	2 (2.2)
Daily	3 (1.0)	1 (1.1)

In female students, the most common indications for self-medication with analgesics were menstrual-related problems (n=192; 80.0%), followed by headache (n=187; 77.9%) and toothache (n=72; 30.0%). In males, the most common discomforts requiring self-medication included headache (n=35; 70.0%), sports injuries (n=22; 44.0%) and hangover (n=15; 30.0%). As expected, statistically significant sex differences were recorded in the indications of menstrual discomforts, present exclusively in female population, and sports injuries and hangover as significantly pronounced indicators for pain self-medication in male population (sports injuries: Pearson's χ^2=55.439; df=1; hangover: Pearson's χ^2=14.220; df=1; p<0.0001 both). Sex differences in the indications for pain self-medication are shown in Table 3.

Male and female students preferred different drugs chosen as self-medication for pain (Table 4). As many as 70% of female students used analgesics from the group of ibuprofen and 30% those from the group of paracetamol, while 24.2% used acetylsalicylic acid. Ketoprofen and diclofenac were taken by a lower proportion of female students (17.9% and 15.8%, respectively). Male students preferred acetylsalicylic acid as self-medication for pain (54.0%), yielding a statistically significant difference from female students (Pearson's χ^2=17.775; df=1; p<0.0001). In addition, male students also used analgesics from the groups of ibuprofen (48.0%), paracetamol (34.0%) and diclofenac (22.4%). There were no other statistically significant sex differences.

Out of 290 subjects having reported self-medication with painkillers in the past year, a high proportion (n=222; 76.6%) used to read package inserts. Of these, there were 190 female and 32 male students, accounting for 79.2% and 64.0% of the female and male study population, respectively. The difference between the female and male students was statistically significant (Pearson's χ^2=5.303; df=1; p=0.021). The group of 68 students not reading package inserts consisted of 50 (20.8%) female and 18 (36.0%) male subjects. Almost half of the study subjects (n=144; 49.7%) having used painkillers in the past year considered they were properly informed on drug side effects. Of these, there

Table 3. Sex differences in the indications for pain self-medication

	Female n (%)	Male n (%)	χ^2 value	p value
Headache	187 (77.9)	35 (70.0)	1.445	0.229
Sports injuries	14 (5.8)	22 (43.0)	55.439	<0.0001
Hangover	24 (10.0)	15 (30.0)	14.220	<0.0001
Menstrual discomforts	192 (80.0)	0 (0)	118.367	<0.0001
Migraine	37 (15.4)	4 (8.0)	1.875	0.171
Toothache	72 (30.0)	11 (22.0)	1.296	0.255
Abdominal pain	48 (20.0)	7 (14.0)	0.969	0.325
Articular pain	17 (7.1)	3 (6.0)	0.076	0.783
Back pain	10 (4.2)	4 (8.0)	1.323	0.250

Table 4. Types of analgesics used by female and male students

Type of drug	Female n (%)	Type of drug	Male n (%)
Ibuprofen	168 (70.00)	Acetylsalicylic acid	27 (54.00)
Paracetamol	81 (33.75)	Ibuprofen	24 (48.00)
Acetylsalicylic acid	58 (24.20)	Paracetamol	17 (34.00)
Ketoprofen	43 (17.90)	Diclofenac	11 (22.40)
Diclofenac	38 (15.80)	Combination of paracetamol, propyphenazone, caffeine and codeine phosphate sesquihydrate (Caffetin)	7 (14.00)
Combination of paracetamol, propyphenazone, caffeine and codeine phosphate sesquihydrate (Caffetin)	32 (13.30)	Metamizole	5 (10.00)
Metamizole	14 (5.80)	Ketoprofen	5 (10.00)
Trospium chloride	7 (2.90)	Tramadol	0
Tramadol	2 (0,.80)	Trospium chloride	0
Indomethacin	1 (0.40)	Indomethacin	0
Rizatriptan	1 (0.40)	Rizatriptan	0

Table 5. Use of other methods of pain relief according to sex

	Female n (%)	Male n (%)	χ^2 value	p value
Rest	206 (85.8)	41 (82.0)	0.481	0.488
Heating pad	46 (19.2)	5 (10.0)	2.399	0.121
Massage	103 (42.9)	24 (48.0)	0.434	0.510
Dressing	96 (40.0)	18 (36.0)	0.278	0.598
Exercise	64 (26.7)	24 (48.0)	8.910	0.003
Herb tea	118 (49.2)	18 (36.0)	2.881	0.090
Cream	39 (16.3)	12 (24.0)	1.715	0.190
Visiting chiropractor	5 (2.1)	2 (4.0)	0.645	0.422
Blockade	0 (0)	1 (2.0)	0	0
Traditional medicine	1 (0.4)	0 (0)	0	0

were 121 female and 23 male students, accounting for 50.4% and 46.0% of the female and male study population, respectively. In contrast, 119 (49.5%) female and 27 (54.0%) male students reported they were not informed of the side effects of the drugs they used for pain relief. There was no statistically significant sex difference in the knowledge about drugs and their side effects.

Study students also reported using other, non-pharmacological options to relieve pain associated with some health problems. Taking rest was the preferred option for 247 (85.2%) subjects, followed by drinking tea (46.9%), massage (43.8%) and applying dressing over the affected part of the body (39.3%). A statistically significant sex difference was recorded in choosing physical activity for pain relief, which was used by as many as 24 (48.0%) male subjects versus only 26.7% of female subjects (Pearson's χ^2=8.910; df=1; p=0.003). Comparison of other methods used by study subjects for pain relief is illustrated in Table 5.

DISCUSSION

Our study results revealed the use of analgesics to be very high among the University of Applied Health Studies students. Taking painkillers in the past year was confirmed by as many as 74.6% of study subjects. Comparable results have been reported by other authors investigating the prevalence and characteristics of self-medication for pain relief on a sample of 291 students in Great Britain, showing that 73% of study students were taking painkillers in the past month (French & James 2008), which is consistent with our finding of 74.6% of study students having used these agents. Our results varied from those recorded in a study conducted among nursing students from Brazil, where 38.8% of students were found to use self-medication for pain relief (Souza et al. 2011). Likewise our study, a higher rate of self-medication among female students was also recorded in Spain (Bassols et al. 2002). A study conducted at the University of Medicine and Medical Sciences in Great Britain yielded similar results on the use of self-medication in male and female students; however, some sex differences were present because female students were more likely to read package inserts and were more careful on using self-medication (James et al. 2006). Similar results have also been reported from the University of Ljubljana, Slovenia. Although there were no statistically significant sex differences in using

painkillers, female students were more careful about doing it and were more likely to seek professional consultation on what drug to choose (Klemec-Ketiš et al. 2011).

The results of the subjective pain self-assessment of study subjects proved very interesting indeed. Using the 1-7 scale, the group of subjects having used painkillers in the past year considered that using painkillers to alleviate pain would be required at the mean intensity of pain of 5.44. On the other hand, in the group of subjects that did not take painkillers in the past year the respective mean intensity of pain requiring some pain relief was set at 6.23. As pain is a subjective sensation, it is difficult to objectify the reasons for this difference; the students not using analgesics probably had a higher pain threshold, which may be underlain by a number of reasons such as anatomic and physiologic differences, variable stimulus intensity, psychological factors (do not like to take drugs and would rather suffer pain), culturological differences (men can stand the pain), modes of coping with pain including attitudes, use of non-medicamentous methods for pain relief, etc.

Men and women prefer different drugs for pain relief. As many as 70.0% of female students used analgesics from the group of ibuprofen, while 33.75% used paracetamol and 24.2% used acetylsalicylic acid. In contrast, 54.0% of male students preferred using acetylsalicylic acid for pain relief (statistically significantly different from female students), followed by analgesics from the groups of ibuprofen (48.0%), paracetamol (34.0%) and diclofenac (22.4%). In Croatia, diclofenac has been usually used for pains caused by sports injuries. As sports injuries are a major indication for pain self-medication in male population, it is no surprise that diclofenac was more frequently used by male students. Studies from all over the world have reported results comparable to our results recorded in a population of students attending the University of Applied Health Studies in Zagreb. Students from Great Britain mostly take paracetamol (50%) and ibuprofen (39%) for pain relief, those from Ethiopia use paracetamol (48.44%) and agents from the group of non-steroidal antirheumatics (NSAR) (42.20%), while as many as 83.86% of students from the USA take ibuprofen for pain relief (Burak & Damico 2000, Gutema et al. 2011, French & James 2008).

Headache was the most common indication for self-medication with painkillers, reported by 76.6% of study students, followed by menstrual-related problems (66.2%) and toothache (28.6%). Headache has been identified as the predominant indication for medicamentous treatment in many studies (Burak & Damico 2000, Gutema et al. 2011, French & James 2008, Souza et al. 2011, James et al. 2006). The high prevalence of headache in student population has also been demonstrated in a study investigating the prevalence of headache and migraine in health care students. The study performed in Iran found 68% of students to suffer from headaches associated with irregular sleep, changing environment, head movements and stress (Menon & Kinnera 2013). A similar study carried out in students in India yielded a headache prevalence of 58.7%. Predictive factors for headache were poor socioeconomic status and year of study (third and fifth years) (Ghorbani et al. 2013). Generally, student population has a higher prevalence of headaches due to stress and inadequate sleep. As many students turn to self-medication due to the shortage of time and because they consider it unnecessary to visit a physician's office for only minor discomforts, it appears reasonable to organize consultations for students on the appropriate use of analgesics near their university premises. As self-medication for pain has also been encouraged by the WHO (WHO 2000), an appropriate approach to the user will enable safer self-medication and making correct decisions on discomfort elimination. Thus, students will assume an active part in taking care of their health status and upgrade their quality of life. Appropriate student education and improved information transfer between professionals and students are the key elements to ensure judicious, quality and knowledge based use of drugs among students. The user can get information on a drug from his/her general practitioner, pharmacist, or from the package insert. Our study revealed that 76.6% of the University of Applied Health Studies students (79.2% of female and 64.0% of male students) used to read package inserts. Comparison with a study on the knowledge, attitudes and use of self-medication among first-year health care students in England (James et al. 2006) showed similar results. In England, package insert was read by 71.6% of students (80% of female and 53% of male students, yielding a statistically significant difference) (James et al. 2006). However, frequently irregular use of drugs suggests that users are not properly informed, pointing to the need of upgrading the transfer of information to make self-medication more judicious, appropriate and based on good knowledge (Sanz et al. 2000). Non-opioid analgesics such as paracetamol and ibuprofen are the most commonly used OTC drugs in western countries such as the USA, Spain, Croatia and Great Britain (Aljinović-Vučić et al. 2005, Burak & Damico 2000, Bassols et al. 2002, PAGB 2005). In Great Britain, paracetamol and ibuprofen accounted for 23% of the overall OTC drug utilization in 2004 (PAGB 2005). Although non-opioid analgesics are easily available to the population at large, they have been associated with a number of side effects. Paracetamol is one of the main causes of drug poisoning (Sheen et al. 2002, Hawton et al. 2004, Morgan et al. 2005), while its high doses have adverse effects on liver function. The use of NSAR such as ibuprofen or acetylsalicylic acid can cause inflamma and ulceration in the gastrointestinal system (Abbott & Fraser 1998). Frequent use of analgesics to alleviate daily headaches can lead to dependence and recurrent headaches upon painkiller withdrawal (Blenkinsopp & Bond 2005). In

1998, Great Britain defined a preventive strategy to control the rate of paracetamol induced poisoning. For this purpose, the legislation was modified as to restrict the amount of tablets that can be bought as an OTC drug. With this measure, the mortality rate due to paracetamol or acetylsalicylic acid overdose was reduced by 22%, while the rate of admissions to departments of nephrology and liver transplantation due to hepatotoxic lesions caused by paracetamol decreased by 30% (Hawton et al. 2004).

Considering all the facts stated above, it appears quite disturbing that only 49.7% of our study subjects reported they were familiar with side effects of the drug they used, suggesting that non-opioid analgesics were not considered as a group of drugs with potential side effects. Similar is the opinion of students from Great Britain, where only 18% and 51% of subjects believed the short-term and long-term use of analgesics to be associated with some risk, respectively (French & James 2008). These data are crucial to highlight the role of student education to instruct them when to seek a physician's or pharmacist's advice. The physician has long been recognized as the authority and consultant on the choice of drug. However, with the increasing proportion of individuals opting for self-medication, the role of the pharmacist has changed. The pharmacist is now the last link in the chain of health care visited by the user before taking drug. Since, the World Health Organization support the self-treatment of pain, proper pharmacist approach through communication and consultations with students can strengthen confidence in seeking advice regarding possible side effects of the drugs. In that case, students will take an active role in caring for their health. That should be taken into account when writing the curriculum of pharmacists education, who will be consultants and educators on a daily basis. The pharmacist should be able to verify the student knowledge regarding drugs and should be able to clearly explain the purpose of the drug, in which dose it needs to be used, which are possible contraindications and how to recognize them. It is the pharmacist's duty to ensure the safest and most efficacious route of drug administration. In the era of self-medication, the consulting role of a pharmacist is of utmost importance since self-medication is usually performed without consulting a physician, therefore the pharmacist is the only professional the user will encounter on choosing the drug for self-medication (Jakševac Mikša 2002).

Using non-pharmacological methods is preferred by medical professionals all over the world as the first-line choice for pain relief; in case of failure, the sufferer will discuss with the professionals on the most efficacious drug and dosage. A study of patient preferences for pain self-medication in a population of 723 subjects in the USA revealed the non-pharmacological methods of pain relief to be used by 68% of study subjects. As many as 40% of them used exercise, 30% reported cooling/ warming the body part involved, 22% used relaxation and 22% massage for pain relief (Vallerand et al. 2005). In the present study, the rate of subjects using massage for pain relief was twofold greater (43.8%), whereas data on subjects using dressings over the affected parts of the body differed considerably (39.3%). A considerably greater proportion of men than women used exercise as a pain relieving technique (48.0% vs. 26.7%).

Different studies have confirmed that senior year students are more likely to use drugs for the purpose of self-medication which is associated with an increase in medical knowledge. In this study were included only full-time first-year students, which is a possible limitation of the study. The research could be extended to full-time students of all three years, in order to compare the attitudes about self-medication for pain relief and characteristics of self-medication among students who have health courses in the curriculum and students without health courses.

CONCLUSION

Taking over the responsibility for one's own health and active role in eliminating the existing health problems have been increasingly recognized all over the world, including Croatia. Self-medication and use of painkillers are also present in students of the University of Applied Health Studies in Zagreb. Self-medication is acceptable if the drug used is free from an unacceptable risk. Inappropriate self-medication and neglecting disease symptoms may lead to symptom worsening and serious health problems associated with even worse pain. Nowadays, the role of the pharmacist in the process of recommendations and selling painkillers is of utmost importance.

The initial results collected in this study assessing the pattern of self-medication in health care students in Croatia can serve as a starting point in future studies investigating the use of painkillers in other population groups.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 466-471 *Original paper*

COMPARISON OF PSYCHOTROPIC DRUG PRESCRIBING QUALITY BETWEEN ZAGREB, CROATIA AND SARAJEVO, B&H

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SUMMARY

***Background**: The purpose of this paper was to compare outpatient consumption and quality of psychotropic drug prescribing between Croatia and Bosnia & Herzegovina 2006-2010.*

***Methods:** Data on drug utilization from Zagreb Municipal Pharmacy and Sarajevo Public Pharmacy were used to calculate the number of defined daily doses (DDD) and DDD per 1000 inhabitants per day (DDD/TID) using the WHO Anatomical-Therapeutic-Chemical methodology.*

***Results:** Total utilization of psychopharmaceuticals increased in both cities; however, it was higher in Zagreb than in Sarajevo throughout the study period. The utilization of psycholeptics increased in Zagreb by 2.4% (from 74.5 to 76.3 DDD/TID) and in Sarajevo by 3.8% (from 62.4 to 64.8 DDD/TID). The utilization of anxiolytics decreased in Zagreb by 2.1% and in Sarajevo by even 18.7%. The utilization of antidepressants increased in both cities with predominance of SSRI over TCA utilization, greater in Sarajevo (96.6%) than in Zagreb (10.2%). The anxiolytic/antidepressant ratio decreased by 11.1% in Zagreb (from 2.87 to 2.55) and by 58.7% in Sarajevo (from 5.66 to 2.34). Outpatient utilization of antipsychotics increased significantly in Sarajevo, predominated by typical ones, whereas in Zagreb the utilization of antipsychotics was stable, predominated by atypical ones.*

***Conclusions:** In Croatia and Bosnia & Herzegovina, there was an obvious tendency to follow western trends in drug prescribing, as demonstrated by the increased use of antidepressants and reduced use of anxiolytics. Despite some improvement observed in the prescribing quality, high use of antipsychotics with dominance of typical antipsychotics in Sarajevo points to the need of prescribing guidelines for antipsychotics.*

***Key words:** psychotropic drugs - prescribing quality - ATC/DDD methodology - Zagreb-Sarajevo*

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INTRODUCTION

Mental disorders pose one of the priority public health problems worldwide. The burden of mental and neurological disorders has been seriously underestimated by traditional epidemiological methods that took into account only mortality, but not disability rate. The proportionate share of total global burden of disease due to neuropsychiatric disorders is projected to rise to 14.7% by 2020 (WHO 2006).

On the other hand, the burden posed by drug costs upon the otherwise inadequate health care resources and rational drug utilization are important segments of every national health policy. The Croatian government was concerned that Croatia appeared to spend more money on medicinal drugs than most other countries in the region (Harvey et al.2004).

According to the Intercontinental Marketing Service (IMS) data, the leading groups of drugs utilized worldwide are cardiovascular drugs, immediately followed by central nervous system (CNS) drugs with a continuous annual rise of 11% (Intercontinental Marketing Service 2007). A similar pattern has been observed in Croatia, with a predominance of cardiovascular drugs followed by CNS drugs (Štimac et al. 2009, Erceg et al. 2005, Štimac et al. 2010).

We embarked upon this study to compare the quality of psychotropic drug prescribing between Zagreb, Croatia and Sarajevo, Bosnia and Herzegovina, as capitals of the two neighboring countries characterized by considerable differences as well as similarities such as common past (former Yugoslavia) and other features (war sufferings, transition countries).

Zagreb accounts for about 18% of the Croatian population and Sarajevo for approximately the same percentage of people inhabiting the Federation of Bosnia and Herzegovina. In addition, Zagreb accounts for 43% of the Croatian health resources and Sarajevo for 30%-40% of Bosnia and Herzegovina health resources (Štimac et al. 2009, Agency for Medicines and Medical Devices of Bosnia and Herzegovina 2011, Official Sarajevo City 2011). Both cities have the county status and represent the trends in their countries as a whole, which makes them highly comparable.

As drug prescribing behavior is known to be influenced by a number of individual factors such as sex, age, cultural background, patient needs and demands, pharmaceutical industry, etc., we were interested to identify the extent to which the Croatian and Bosnian prescribing habits follow modern principles of psychopharmacotherapy (Štimac et al. 2009) .

The aims of the study were: 1) to determine the outpatient utilization of psychiatric drugs in Zagreb and Sarajevo; 2) to compare the outpatient utilization of psychiatric drugs between the two cities; and 3) to assess the quality of psychopharmaceutical prescribing using the World Health Organization Anatomical-Therapeutic-Chemical classification system (ATC)/ Defined Daily Doses (DDD) methodology (ATC/DDD methodology) and Eurostat ratio indicators (WHO 2009).

METHODS

Data on the outpatient utilization of psycholeptics and psychoanaleptics (ATC groups N05 and N06) in both cities were received from pharmacies and collected during 2006, 2007, 2008, 2009 and 2010. Data are expressed as defined daily doses *per* thousand inhabitants *per* day (DDD/TID). Using the ATC/DDD methodology, the data obtained can be compared with other settings and between different time periods (WHO 2009).

On DDD/TID calculation, data from the 2001 census were used, according to which the population of Zagreb was 770 058 (Croatian Bureau of Statistics 2011). As for Sarajevo, we used the latest data published by the Federation of Bosnia and Herzegovina Federal Office of Statistics, according to which the population of Sarajevo County was 423 645 (FBiH Federal Office of Statistics 2011). Total outpatient utilization of ATC N05 and N06 prescription drugs, utilization distribution of these groups of drugs at secondary, tertiary and quarterly level, and consumption of individual drugs were analyzed.

The Drug Utilization 90% (DU90%) method and Eurostat ratio indicators were used on prescribing quality evaluation (EURO-MED-STAT Group 2003).

RESULTS

The utilization of psycholeptics increased in Zagreb by 2.4% (from 74.5 to 76.3 DDD/TID) and in Sarajevo by 3.8% (from 62.4 to 64.8 DDD/TID) (Table 1). The utilization of antidepressants was on an increase in both cities. It increased by 10.2% (from 18.6 DDD/TID in 2006 to 20.5 DDD/TID in 2010) in Zagreb and by far more (96.6%) in Sarajevo (from 8.9 DDD/TID in 2006 to 17.5 DDD/TID in 2010). Analysis of trends in Zagreb revealed continuous rise in the utilization of antidepressants until 2008, followed by a 6.8% decline in 2010. In Sarajevo, the rising trend was continuously recorded, being more pronounced in 2007 compared to 2006 and in 2009 compared to 2008.

The utilization of anxiolytics was on a decrease in both cities. It decreased by 2.1% in Zagreb and significantly more, by 18.7%, in Sarajevo. Analysis of trends in Zagreb revealed a rising trend until 2008, followed by a decline. Although a greater decline in the utilization of anxiolytics was recorded in Sarajevo, the decreasing trend was not continuous.

In total antidepressant and anxiolytic utilization during the 2006-2010 period, the utilization of anxiolytics exceeded the utilization of antidepressants both in Zagreb and in Sarajevo. Antipsychotic drugs are divided into two subgroups for this overall analysis. Outpatient utilization of atypical antipsychotics including clozapine, olanzapine, quetiapine, sulpiride, ziprasidone, zuclopentixole and risperidone increased in both cities. The utilization of typical antipsychotics showed a declining tendency in Zagreb, whereas in Sarajevo a significant increase was recorded (Table 1).

Table 1. Utilization of psychiatric drugs in Zagreb and Sarajevo during the 2006-2010 period expressed as DDD/TID

		DDD/TID				
	Year	Psycholeptics N05	Antipsychotics N05A Typical	Atypical	Anxiolytics N05B	Antidepressants N06A
Zagreb	2006	74.5	2.8	5.5	53.4	18.6
	2007	77.5	2.9	5.9	54.4	20.2
	2008	82.0	2.8	6.1	57.4	22.0
	2009	76.1	2.7	5.9	52.2	20.8
	2010	76.3	2.5	5.9	52.3	20.5
Sarajevo	2006	62.4	3.4	3.5	50.4	8.9
	2007	57.2	2.8	2.4	45.8	11.8
	2008	69	5.1	5.4	51.9	11.3
	2009	61.6	5.9	6.4	39.5	16.9
	2010	64.8	6.4	7.7	41.0	17.5

Table 2. Psycholeptics and psychoanaleptics within Drug Utilization 90% (DU90%) segment expressed as DDD/TID in Zagreb in 2010

Number	Drug name	DDD/TID	Share (%)
1	Diazepam	24.55	25.35
2	Alprazolam	14.93	15.42
3	Zolpidem	12.58	12.99
4	Oxazepam	7.13	7.36
5	Lorazepam	5.20	5.37
6	Sertraline	5.17	5.34
7	Paroxetine	3.82	3.95
8	Olanzapine	2.78	2.87
9	Escitalopram	2.34	2.42
10	Nitrazepam	2.20	2.27
11	Citalopram	2.05	2.11
12	Fluvoxamine	1.87	1.93
13	Fluoxetine	1.76	1.82
14	Promazine	0.99	1.02
DU90% 1-14		87.36	90.21
Others 15-49		9.48	9.79
Total		96.84	100.00

Table 3. Psycholeptics and psychoanaleptics within Drug Utilization 90% (DU90%) segment expressed as DDD/TID in Sarajevo in 2010

Number	Drug name	DDD/TID	Share (%)
1	Diazepam	22.96	27.87
2	Bromazepam	13.12	15.93
3	Paroxetine	5.78	7.02
4	Fluoxetine	4.9	5.95
5	Zolpidem	4.66	5.66
6	Sertraline	4.06	4.93
7	Nitrazepam	4	4.86
8	Lorazepam	2.66	3.23
9	Olanzapine	1.96	2.38
10	Clozapine	1.7	2.06
11	Haloperidol	1.62	1.97
12	Sulpiride	1.58	1.92
13	Amitriptyline	1.38	1.68
14	Risperidone	1.28	1.55
15	Promazine	1.24	1.51
16	Ziprasidone	1.18	1.43
DU90% 1-16		74.08	89.92
Others 17-31		8.3	10.08
Total		82.38	100.00

Outpatient drug utilization within and beyond DU90% segment in 2010 was compared between Zagreb (Table 2) and Sarajevo (Table 3). Fourteen and 16 drugs fell under DU90% segment in Zagreb and Sarajevo, respectively. In Zagreb, four benzodiazepines and two hypnotics, six antidepressants, one third-generation antipsychotic (olanzapine) and one first generation antipsychotic (promazine) were present within DU90% segment. The most used benzodiazepines were diazepam and alprazolam. The most used antidepressants were sertraline and paroxetine, both SSSRIs.

In Sarajevo DU90% profile comprised of 16 drugs – three benzodiazepines and two hypnotics, four antidepressants, and seven antipsychotics.

Haloperidol among typical, and olanzapine among atypical, were the most used antipsychotic drugs in Sarajevo (Table 2, Table 3).

DISCUSSION

In this retrospective study we compared the utilization of CNS drugs. Study results pointed to differences in the psychopharmaceutical utilization pattern in primary health care between Zagreb County and Sarajevo Canton. The differences were partly attributable to different socioeconomic and health policy factors in the two settings.

DU90% is a simple and rapid but rough method for assessing drug prescribing in routine healthcare settings. It enabled us to highlight the drugs most used in each year and to determine the effect of the list update: almost immediately after the update, the newly introduced drugs fell into the DU90% profile. The number of drugs in the DU90% profile can also provide valuable information on the prescribing habits in the growing drug market (Štimac 2009, EURO-MED-STAT Group 2003, Marković-Peković et al. 2010, Bergman et al. 1998).

Analysis of DU90% segment in Zagreb in 2010 revealed utilization of even 5 benzodiazepines including 4 anxiolytics and one hypnotic (nitrazepam). Zolpidem belongs to a new generation of benzodiazepine related hypnotics, which is currently recommended as therapy for insomnia; in Zagreb, the utilization of zolpidem was on an increase from 2003 (from 8.1 to 12.99 DDD/TID) (Andersen & Frydenberg 2011). A similar trend was recorded in Sarajevo, however, the overall share of benzodiazepines within DU90% segment was lower than that found in Zagreb. Along to the high utilization of zolpidem, a high utilization of nitrazepam was also recorded in Sarajevo.

In Zagreb, even 6 of 6 antidepressants within DU90% segment were from the SSRI group. The utilization of escitalopram (although on the Supplementary List of the Croatian Institute of Health Insurance, CIHI) exceeded the utilization of citalopram (CIHI Main List), along the lines of the latest research suggesting that escitalopram is more efficient than citalopram and other SSRIs or SNRIs according to health and economic indicators. Escitalopram has been associated with lower cost and lower health care utilization, primarily owing to less common and shorter hospitalizations relative to citalopram. In addition, patients administered escitalopram have to switch to other antidepressants less frequently than those taking citalopram (Wu et al. 2012,

CIHI 2006). In Sarajevo, 3 of the 4 antidepressants were from the SSRI subgroup (paroxetine, fluoxetine and sertraline), along with one tricyclic amitriptyline, which is according to current knowledge, responsible for more side effects than SSRI (Štimac et al. 2009, Marković-Peković et al. 2010, Sauer et al. 2003).

In Zagreb, olanzapine was the antipsychotic falling within DU90% segment; it is the third generation antipsychotic which is included in the CIHI Main List but can only be prescribed if recommended by a psychiatrist. Total antipsychotic utilization was stable throughout the study period (8.3 DDD/TID in 2006 *vs*. 8.4 DDD/TID in 2010), with a predominance of atypical antipsychotics. Newer atypical antipsychotics have a number of advantages over old typical antipsychotics, such as better tolerability and a significantly lower incidence of extrapyramidal side effects (Jakovljević 2001, Štimac et al. 2009). The third generation antipsychotics have become the standard of antipsychotic pharmacotherapy and the first line treatment for schizophrenia (Jakovljević 2009, Thibaut 2014), although the results of some pragmatic clinical trials have delivered controversial messages about comparative efficacy and effectiveness of the new generation antipsychotics. Personalized medicine in psychiatry is not possible without the availability of enough number of different modern antipsychotics (Jakovljević 2009).

In Sarajevo, even 7 antipsychotics including 2 typical antipsychotics were within DU90% segment, which was quite surprising for outpatient drug utilization at the primary health care level. During the 5-year period, the outpatient utilization of antipsychotics increased by 104% (from 6.9 DDD/TID in 2006 to 14.1 DDD/TID in 2010). The utilization of typical antipsychotics was still too high, although their rise during the study period was lower compared to the rise in the utilization of atypical antipsychotics (88% *vs*. 120%), similar to Slovenia, Serbia and Montenegro; however, in these countries, the increase in the utilization of typical antipsychotics was considerably lower or almost stopped (Medicines and Medical Devices Agency of Serbia 2007, Montenegro Health Insurance Fund 2008, Divac et al. 2006, Furst & Kocmur 2003).

The recent inclusion of a number of antipsychotics on the List of Drugs approved by the Sarajevo Canton Institute of Health Insurance must have been the main reason for the increased utilization of antipsychotics in Sarajevo, as it enabled wide use of these drugs (Sarajevo Canton Institute of Health Insurance 2009). In addition, a project of mental health improvement, with special reference to posttraumatic stress disorder (PTSD) patients, was launched at the time; along with socioeconomic status (a high rate of unemployment), PTSD could also add to the increased utilization of antipsychotics (Sarajevo Canton Institute of Health Insurance 2007). The citizens of Sarajevo were long exposed to war actions, which certainly contributed to the high prevalence of mental disorders in comparison with Zagreb citizens. Numerous studies have confirmed the association of exposure to war actions and prevalence of mental disorders, PTSD and major depression in particular; the more so, a study conducted in five Balkans countries showed the prevalence of these disorders in Bosnia and Herzegovina to exceed the prevalence recorded in other countries involved (Priebe et al. 2010).

The ratio of anxiolytics to antidepressants has also been used as an indicator of psychopharmaceutical prescribing quality in a particular setting, whereby antidepressants as etiological therapy should prevail (EURO-MED-STAT Group 2003, Štimac et al. 2009). In Zagreb, the anxiolytic/antidepressant ratio decreased from 2.87 in 2006 to 2.55 in 2010. The decrease in the utilization of anxiolytics with symptomatic action and the increased utilization of antidepressants with etiologic action points to improved psychopharmaceutical prescribing quality. Although this ratio decreased by 11.1% during the study period, and by even 65.1% from 2001, it still remained unfavorable in comparison with Scandinavian countries, where it ranges from 0.7 in Finland, through 0.4 in Norway and Denmark, to 0.3 in Sweden, and also with Slovenia (0.5), while being better in comparison with the Republic of Srpska, Bosnia and Herzegovina (8.8) and Serbia (10.7) (Divac et al. 2004, Divac et al. 2006, Norwegian Institute for Public Health 2011, Svab et al. 2011, Štimac et al. 2009). In Sarajevo, the anxiolytic/antidepressant ratio decreased by 58.7% during the study period (from 5.66 in 2006 to 2.34 in 2010). This great and abrupt reduction in the utilization of anxiolytics must have resulted from the efforts invested by the Bosnia and Herzegovina Agency for Drugs and Medicinal Products and strict inspection in public pharmacies because the principle of prescription drug issuing used to be obviated quite frequently, so that these relatively inexpensive drugs could be bought as over-the-counter medicines. In private sector, this practice then persisted for some time, however, showing a declining tendency. It was one of the private sector measures to attract these patients; when they could not buy the drug without prescription in public pharmacy, they used to go to private pharmacy to get the drug (Agency for Drugs and Medicinal Products of Bosnia and Herzegovina 2008). The psychopharmaceutical prescribing quality has been influenced by the specific socioeconomic features in these countries.

The fact that the outpatient drug utilization data were systematically collected in Croatia, whereas in Bosnia and Herzegovina the issue is not regulated by law, could be perceived as one of the study limitations (By-Law on the Type of Data and Reporting on Drug Utilization 2005). This may be one of the obstacles in conducting studies like this, which can help improve the prescribing habits.

Until 2001, only economic indicators of drug consumption were monitored in Zagreb and Croatia; therefore the problem of benzodiazepine overutilization

because of their low price could not be identified. Upon switching to the new methodology of monitoring drug utilization and introducing the WHO ATC/DDD method, the problem has emerged and an array of public health and regulatory measures have been launched, i.e. education of primary health care physicians on the rational use of benzodiazepines and inclusion of SSRI on the Main List of Drugs (By-Law on the Type of Data and Reporting on Drug Utilization 2005). These interventions have resulted in a reduced utilization of benzodiazepines and improved prescribing quality in Zagreb.

Another limitation of this study was the limitation of the DDD methodology itself, as the defined daily dose does not necessarily reflect the recommended or prescribed daily dose. This methodology provides only a rough estimate of consumption and not an exact picture of actual use (Bergman et al. 1998, EURO-MED-STAT Group 2003, Štimac et al. 2009).

CONCLUSION

Comparison of psychopharmaceutical utilization in Zagreb County and Sarajevo Canton during the study period (2006-2010) revealed some similarities as well as some significant differences. Although the utilization of anxiolytics was found to have decreased in both cities, it was still too high and irrational due to the high utilization of benzodiazepines. The utilization of antidepressants increased in both cities, whereby the utilization of TCA was lower in Zagreb as compared with Sarajevo. The utilization of SSRI was higher in Zagreb, pointing to better quality of antidepressant prescribing in this city.

Updating the list of drugs with SSRI antidepressants is a rational and unavoidable decision, paving the way for implementation of clinical guidelines for the treatment of mental disorders. It also influenced the anxiolytic/antidepressant ratio, which was found to have improved considerably in both cities in 2010 as compared with previous years, as an indicator of more favorable prescribing habits in the treatment of anxiety and depression as the two most common mental disorders managed by general practitioners.

The utilization of psycholeptics increased in Sarajevo during the 5-year study period; while the utilization of anxiolytics was significantly reduced, the utilization of antipsychotics showed a rising tendency.

The outpatient utilization of antipsychotics was too high and irrational considering the high share of typical antipsychotics within DU90% segment and the fact that these drugs can only be prescribed to the general population if recommended by a psychiatrist. The high utilization of antipsychotics in Sarajevo was probably related to the high prevalence of PTSD.

In Croatia and Bosnia and Herzegovina, there is an obvious tendency to follow western trends in drug prescribing, as demonstrated by the increased utilization of antidepressants and reduced use of anxiolytics. Despite some improvement observed in the prescribing quality, high use of antipsychotics with dominance of typical antipsychotics in Sarajevo points to the need of prescribing guidelines for antipsychotics in Bosnia & Herzegovina. However, greater efforts need to be invested to additionally improve the prescribing quality in both countries.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 472-475 *Original paper*

IMPLEMENTATION OF THE PROGRAM OF PREVENTIVE EXAMINATIONS AT PRIMARY HEALTH CARE IN THE CITY OF ZAGREB 2009-2013

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SUMMARY

Background: *The program covered all persons who had not been in contact with a physician for two years or had failed to notice symptoms themselves or to timely respond to the symptoms observed. The aim of the present study was to analyze the results of the program and try to draw conclusions regarding the necessity further implementation.*

Subjects and methods: *This paper analyzes data on a cohort of 1375 subjects aged 45+, collected on preventive examinations by family physicians during the 2009-2013 period.*

Results: *Results show 24.4% smokers and 15.5% former smokers. Up to three alcoholic drinks per week consumed 18.5% respondents (27.8% male and 11.2% female). Overweight (body mass index 25-30) was recorded in 50.6% and 38.6%, obesity (body mass index >30) in 30.1% and 29.4%, hypertension in 14.6% and 11.8%, isolated systolic hypertension in 20.5% and 17.4%, and isolated diastolic hypertension in 3.3% and 3.0% of male and female subjects, respectively. Suspicion of one or more newly diagnosed disease was recorded in 52.9% (95% CI 50.2-55.5) of study subjects. Fifty-four subjects (7.4%; 95% CI 5.5-9.3) were suspected to have neoplasm and they were immediately referred for further diagnostic evaluation.*

Conclusions: *Timely manner suspicion of malignant disease is of crucial influence on the course of treatment and outcome of the disease. The study results confirm the importance of continuing the implementation of prevention programs.*

Key words: *risk factors - chronic noncommunicable diseases - preventive examinations - cardiovascular diseases*

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INTRODUCTION

Raising awareness of the inappropriate habits and behavior patterns as risk factors that influence the occurrence of chronic noncommunicable diseases is one of the continuous tasks of public health professionals. It is estimated that 86% of deaths and 77% of disease in the European region are caused by chronic noncommunicable diseases. In the next decade, the number of deaths caused by chronic noncommunicable diseases will increase by 17%, thus continuously raising health care costs (Poljičanin et al. 2012a).

Cardiovascular diseases are the leading cause of death in Croatia (Croatian National Institute of Public Health, 2013). In the City of Zagreb in 2013, 46% of the leading cause of death was cardiovascular disease with 3827 deaths and a rate of 484.4 deaths per 100,000 inhabitants. In primary health care, cardiovascular disease ranked the second most common reason for visiting family physician, with a share of 12.3% and 303,288 diagnoses, immediately following respiratory disease (Dr Andrija Štampar Institute of Public Health, 2013).

Despite the well organized public health network, a comprehensive system for cardiovascular disease monitoring and interventions does not exist (Džakula et al. 2009). Program Implementation of the Preventive Examinations in Primary Health Care in the City of Zagreb Program is part of a complex network of preventive activities carried out by a range of stakeholders in health care system. In 2004, the Ministry of Health and Welfare and the Croatian Institute of Health Insurance launched a program of preventive examinations of insured persons older than 45, paying the general practitioner/family medicine teams for the service provided. Since then, the program has been continuously carried out every year with some changes in the contents and scope of screening, age limit of the insured, or the method of financing the examiners, i.e. general practitioners/family physicians.

The aim of this paper is to analyze the results of the program in the default period and to try to conclude on the necessity of its continuation in the same or modified form.

SUBJECTS AND METHODS

All persons older than 50 who had not visited their family physicians for at least two years were invited for free physical examination and laboratory testing. A total of 1375 subjects were examined and interviewed during the 2009-2013 period.

Insured persons were informed about the review through media campaign posters in health centers or personally invited by their family physicians. During the

examination, the physician takes personal and family medical history, previous and present diseases, habits, especially smoking habits and consumption of alcohol drinks. Body height, body weight, blood pressure and body mass index (BMI) were determined and physical examination performed in each study subject. In women, breast palpation, mammography and Pap test findings in the past 3 years were recorded. Special attention was paid to nonspecific signs of malignancy and included targeted conversation and digital rectal examination. Laboratory testing included blood cholesterol, hemoglobin and glucose, semi-quantitative urine analysis and occult blood test. Finally, the physician diagnosed the possible newly discovered or suspected diseases as well as the measures taken. The individual forms were collected at Dr Andrija Štampar Institute of Public Health and data were entered in the respective database. Data were analytically processed and evaluated at the City of Zagreb level.

The results were expressed as percentage of prevalence and 95% confidence interval (95% CI). Statistical analyses were performed using the SPSS software (version 14.01; License: Croatian National Institute of Public Health).

RESULTS

During the 2009-2013 period, 1375 persons underwent preventive examinations. The number of examinations continuously declined. The highest number of examinations (n=762) were performed in 2009, followed by 317 examinations in 2010, 102 examinations in 2011, 112 examinations in 2012 and 82 examinations in 2013. A total of 156 family physicians took part in conducting the review. The number of physicians that conducted preventive examinations was also on a continuous decline. Sixty-six physicians were included in the study in 2009, 53 in 2010, 17 in 2011, 13 in 2012 and only seven in 2013. During the 5-year period, 1736 newly diagnosed and suspected disease were detected in 727 subjects. Due to the reduced total number of participants, the number of newly detected and suspected disease decreased with time; 958 diseases were diagnosed in 2009 versus 168 diseases in 2013 (Table 1).

The mean age of study subjects was 61.5 years. Although the program has been designed for people older than 50, 59 (4.3%) subjects were younger than 50. Almost half of the participants (n=616; 44.9%) were in the 50-59 age group and one-third (n=397; 28.9%) in the 60-69 age group (Table 2). The analysis included 601 men and 774 women, yielding a 44:56 male to female ratio.

There were 24.4% of smokers and 15.5% of former smokers (Table 3). Taking up to three alcoholic drinks per week was reported by 18.5% respondents (27.8% male and 11.2% female) (Table 4). Overweight (BMI 25-30) was present in 50.6% and 38.6%, and obesity (BMI >30) in 30.1% and 29.4% of male and female

Table 1. Number of preventive examinations, family doctors as examiners, newly detected suspected diseases and persons with newly detected deseases according to years

	2009	2010	2011	2012	2013	Total
Preventive examinations	762	317	102	112	82	1375
Family doctors as examiners	66	53	17	13	7	156
Newly detected diseases	958	398	72	140	168	1736
Persons with newly detected diseases	417	160	39	50	61	727

Table 2. Subject distribution according to age groups and gender

Age (yrs)		<50	50-59	60-69	70-79	80-89	≥90	Total
Men	n	25	265	179	110	22	0	601
	%	4.2	44.1	29.8	18.3	3.7	0	100.0
Women	n	34	351	218	132	36	1	772
	%	4.4	45.5	28.2	17.1	4.7	0.1	100.0
Total	N	59	616	397	242	58	1	1373
	%	4.3	44.9	28.9	17.6	4.2	0.1	100.0

Table 3. Smoking habit according to gender

		Non smokers	Former smokers	<10 cigarettes/day	<20 cigarettes/day	>20 cigarettes/day	Unknown	Total
Men	n	285	139	26	78	59	14	601
	%	47.4	23.1	4.3	13.0	9.8	2.3	100.0
Women	n	518	74	68	81	23	10	774
	%	66.9	9.6	8.8	10.5	3.0	1.3	100.0
Total	N	803	213	94	159	82	24	1375
	%	58.4	15.5	6.8	11.6	6.0	1.7	100.0

Table 4. Alcohol consumption prevalence and number according to gender

		Does not drink	Abstinent	2-3 drinks/ week	1-2 drinks/ day	≥3 drinks/ day	Unknown	Total
Men	n	274	167	84	19	19	41	601
	%	45.6	27.8	14.0	3.2	3.2	6.8	100.0
Women	n	620	87	14	4	4	42	774
	%	80.1	11.2	1.8	0.5	0.5	5.4	100.0
Total	N	894	254	98	23	23	83	1375
	%	65.0	18.5	7.1	1.7	1.7	6.0	100.0

Table 5. Body mass index according to gender

		Underweight	Normal weight	Overweight	Moderate and severe obesity	Very severe obesity	Total
Body mass index (kg/m-2)		<18.5	18.5-24.9	25.0-29.9	30.0-39.9	≥40.0	
Men	n	4	110	299	172	6	591
	%	0.7	18.6	50.6	29.1	1.0	100.0
Women	n	5	238	294	208	16	761
	%	0.7	31.3	38.6	27.3	2.1	100.0
Total	N	9	348	593	380	22	1352
	%	0.7	25.7	43.9	28.1	1.6	100.0

Table 6. Hypertension according to gender

Diastolic blood pressure				Men	Women	Total	
≤90 mm Hg	Systolic blood pressure	≤140 mm Hg	n	354	502	856	Normotension
			%	61.6	67.8	65.1	
		>140 mm Hg	n	118	129	247	Isolated systolic hypertension
			%	20.5	17.4	18.8	
>90 mm Hg	Systolic blood pressure	≤140 mm Hg	n	19	22	41	Isolated diastolic hypertension
			%	3.3	3.0	3.1	
		>140 mm Hg	n	84	87	171	Hypertension
			%	14.6	11.8	13.0	
Total measured			N	575	740	1315	
			%	100.0	100.0	100.0	

subjects, respectively (Table 5). Hypertension (systolic pressure >140 mm Hg and diastolic pressure >90 mm Hg) was found in 14.6% and and 11.8%, isolated systolic hypertension in 20.5% and 17.4%, and isolated diastolic hypertension in 3.3% and 3.0% of male and female subjects, respectively (Table 6). Digital rectal examination was performed in 803 subjects and detected pathologic phenomena in 10.4% of female and 19.2% of male subjects.

Suspicion of one or more newly diagnosed diseases was recorded in 52.9% of study subjects (95% CI 50.2-55.5). In total, 727 newly diagnosed diseases were suspected, including disorders of lipoprotein metabolism (n=162; 22.3%), followed by hypertension (n=71; 9.8%), obesity (n=57; 7.8%) and non-insulin dependent diabetes mellitus (n=43; 6.3%). Neoplasms were suspected in 54 subjects (7.4%; 95% CI 5.5-9.3) and they were immediately referred for further diagnostic evaluation.

DISCUSSION

In 2003, the Croatian Adult Health Survey (CAHS) for cardiovascular risk was implemented as part of the activities aimed at health promotion. In 2008, in cooperation with community nurses, the project survey was broadened (Džakula et al. 2009). In CroHort study 5-year cumulative incidence was 5.6%, respectively 1% of the Croatian adult population develops diabetes each year (Poljičanin et al. 2012b). Results of the present study yielded a slightly higher incidence (6.3%). According to the CroHort study, the prevalence of obese adults in 2008 was 25.3% for men and 34.1% for women (Musić Milanović S et al. 2012). Taking into account the limited level of comparability, as elderly people were included in the present study, there was a higher proportion of obese men (29.1%) and a slightly lower proportion of obese women (27.3%).

In 2008, the prevalence of smoking was 25.3% in men and 22.4% in women. Six years later, the prevalence was slightly higher in men (27.1%) and unchanged in women (22.3%). Analysis of the habit distribution according to gender revealed that only 21.8% of men and 48.2% of women had never smoked, while all others were smokers or former smokers (Samardzić et al. 2012), which is in contrast to our results on a much higher proportion of nonsmokers (47.4% of men and 66.9% of women).

Therefore, the subjectivity of study participants should be taken into account. Sometimes persons describe themselves as nonsmokers, although being current, former or occasional smokers.

Alcohol consumption is traditionally part of human culture in many regions of the world, including Croatia. In a previous study, taking alcohol drinks was reported by 13.4% of men older than 65 and only 2.2% of the age-matched women (Vitale et al. 2012). Our study showed much higher shares, i.e. taking up to three alcoholic drinks per week was reported by 41.8% of male and 13% of female subjects.

If the pattern of hypertension management such as awareness, treatment and control continues until 2022, 80% of patients with treated hypertension will have controlled blood pressure levels with a potential annual saving of about 50,000 major cardiovascular events (Falaschetti et al. 2014). According to the Canadian Health Measures Survey that included 1706 Quebec inhabitants, the prevalence of hypertension in the ≥65 age group rose to 69.0% in women and 61.7% in men. In Canada, nearly one of four adults was diagnosed with hypertension in 2007-2008 (Blais et al. 2014). In women, both long-term overweight and recent overweight (in the last 5 years) were found to be significantly associated with the development of hypertension, whereas in men it was true only for long-term overweight (Ivičević Uhernik et al. 2012). In women aged 50-64, hypertension was associated with an increased risk of death compared to normotensive subjects (Mihel et al. 2012). Even 9.8% of subjects were not aware of their hypertension and the necessity of treatment.

CONCLUSIONS

The Program covered all persons who had not visited their physician for two years or had not noticed symptoms or timely responded to the symptoms observed themselves. Detecting cardiovascular risk, cardiovascular disease and malignant state as early as possible is extremely important, confirming the public health significance of such programs.

The number of preventive examinations decreased in the number of checkups and number of physicians taking part in program implementation. Nevertheless, the high number of newly discovered diseases and conditions indicated the need to continue program implementation. Certainly, it is necessary to additionally explore the reasons for the fall in the rate of responders, to change the criteria for patient inclusion and to improve the contents of the program.

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Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 476-484 *Original paper*

SCHOOL HEALTH SERVICES IN THE CITY OF ZAGREB – DO WE MEET ADOLESCENTS' NEEDS?

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SUMMARY

Background: *School health services (SHS) have in Croatia long tradition, established organizational structure, defined program and educated staff. The program is limited to the preventive activities. The aim of the study was to investigate the satisfaction of the children, school staff and parents with existing school health services in the City of Zagreb.*

Subject and methods: *The structured questionnaire was sent to the primary and secondary schools in the City of Zagreb, which were selected using random sample method. The questionnaires were anonymous and filled in supervised by class masters. In the secondary schools the structure of schooling was respected. Questionnaires were filled by 448 pupils from primary, 551 from secondary schools, by 596 parents and 595 teachers.*

Results: *In primary schools pupils rated SHS more available and accessible, staff complaisant and responsible, counselling being useful and justified, confidentiality respected higher than pupils from secondary schools ($p<0.001$). Teachers from primary and secondary schools perceived SHS as valuable school partners (88.9% and 82.3%). Teachers from primary and secondary schools (88.9% and 88.1%) and parents (78.3% and 67.5%) stated that SHS could not be replaced by GPs or paediatricians. Primary school pupils felt that most common problems were injuries and vocational counselling, secondary school pupils assessed behavioural and sexual related problems as mostly challenging. Satisfaction with the SHS response to the most challenging problems was rated higher by teachers from primary schools ($p<0.001$ for learning difficulties, chronic diseases, bullying and vocational counselling), by parents for learning difficulties and vocational counselling, but no significance was found for pupils' satisfactions.*

Conclusion: *SHS in Zagreb are recognized as vital and necessary partners for schools, available and accessible for pupils, teachers and parents, especially for primary schools. Counselling is highly rated by all respondents, confidentiality considered as respected, and the problem of the most common challenges as successfully solved.*

Key words: *school health services – availability - young people – confidentiality – prevention - Croatia*

* * * * *

INTRODUCTION

The adolescence is period in human life between the onset of puberty and the adulthood, starting from 10-13 yrs and lasting till 18-19 yrs. It is often considered as an emotionally and physically intensive and very stressful period. Beyond all the physical, emotional and social transformations, in adolescence the behavioural patterns are formed and lifestyles accepted. Social and economic development affected morbidity and mortality all over the world (Patton and al.2009). The leading causes of adolescent mortality are accidents (death from unintentional injury), followed by neoplasms (Coric & Miller 2013). Additional morbidity is related to risky behaviour including substance use (tobacco, alcohol and drugs), risky sexual behaviour, poor nutrition and inadequate physical activity. One third of adolescents engage in at least one of these high-risk behaviours. The beginning of many mental health disorders is in adolescence. This is not true just for the serious mental health problems, but for the variety of the health behaviours that may influence the adult behaviour, even the onset of diseases in the adult life (Evans et al. 2005).

Surveys done in the past several decades using nationally representative samples revealed that more than 85% of adolescents in Croatia have used alcohol in the last 30 days and more than 50% have engaged in binge drinking (i.e., consuming more than five drinks in one sitting) in the same period of time (Hibell et al. 2011).

Tobacco use also is common during adolescence. Lifetime use of tobacco has decreased over the past decade, but 70% of adolescents have used tobacco at least once. The reported lifetime use of marijuana decreased between 2003 and 2007 and since then has been stabilized (Hibell et al. 2011).

Croatian adolescents are less engaged in the early sexual intercourse in comparison to other European countries and the condom use, although rather high (82% of 15 yrs. old used condom at the last intercourse), could be higher to be on the safe side for the STI prevention (Currie et al 2012, Kuzman et al. 2007).

In the European strategy for child and adolescent health and development is stated: "Children are our investment in tomorrow's society. Their health and the way in which we nurture them through adolescence into adulthood will affect the prosperity and stability of countries in the European Region over the coming decades". Although document does not imply specific separate services for school children and youth, it is suggested that youth-friendly counselling and health services for reproductive and mental health and other health problems are needed (WHO 2005).

Today the health care for school children and youth is aiming at enabling young people's undisturbed growth and physical, mental and emotional development. The main tasks are focused not only at physical morbidity, but at the complex contextual influences in childhood

and adolescence (WHO 2012). For developmental as well as epidemiological reasons, young people need youth-friendly models of primary care. Over the past two decades, much has been written about problems and barriers young people face in accessing health care (Tylee et al. 2007).

The school health services have in Europe and in Croatia long tradition. School health care programs aiming at the prevention, the early detection and the appropriate treatment of ill-health in the young population contributed strongly and consistently to the decreasing mortality and morbidity rates in this age group during the last decades. School health care contributes strongly to young people achieving their full potential on physical, cognitive, emotional and psychosocial levels (Lancic 2009). The first school physician was appointed in 1840 in Sweden. The first school physician in Croatia was appointed in Zagreb, in 1893. In 1923 in Zagreb was established the first school medicine office, as an independent health institution for 5,000 pupils (Kesic 1961, Loncar Dusek 1994, Hofgräff & Fatović-Ferencic 2012). Across the time, the school medicine offices became responsible for the comprehensive health care for the school children, being part of the primary health care. The professionals working in the offices were school medicine specialists and nurses. The medical specialization for physicians started as a three-year postgraduate education in 1951 and is existing till now days (today the specialization lasts 4 years and is titled "school and adolescent medicine").

Beginning of the 90ties brought the changes in the health laws and by-laws. All citizens were entitled to the free choice of personal practitioner in the primary health care, meaning that school children could choose a paediatrician or general practitioner as a person responsible for curative part of the care. This lead to the disintegration of the comprehensive health care school health offices had provided and according to the Minister of health decision school health offices have been disintegrated in 1997. School health services became part of the institutes of public health, providing preventive health care measures according to the annual plan and program. Curative part of the care was shifted to the local paediatrics or general practitioners' offices (Prebeg 1998).

At the present, school health services are situated in 21 County Institutes of Public Health, with the National Public Health Institute having central and coordinating role. School health services embrace altogether approximately 180 medical teams with school medicine specialist and nurse, being responsible for 3,800-4,000 school children and youths. The areas of work embrace a wide range of preventive measures, the annual program being developed and enacted at the national level, according to Health Care Measure Plan and Program (OG126/2006).

To emphasize are the following activities: preventive health check-ups and other preventive examinations; screening; vaccination; counselling for pupils, parents and school staff; health education; care for pupils with special needs integrated in the learning process. In addition, school doctors are often involved in multidisciplinary projects at the national or local level. Being aware that today organization and content of the school health services in Croatia have advantages but disadvantages as well, we wanted to explore the perception of the services by the population whom the care is devoted to.

Aims of the Study

To investigate perception and differences in perception of school health services among pupils, parents and teachers in primary and secondary schools.

SUBJECT AND METHODS

We investigated the satisfaction of the children, school staff and parents with existing school health ser in the City of Zagreb. A questionnaire was constructed containing 21 questions, slightly different in wording for different groups. Primary and secondary schools were randomly selected, preserving in the secondary schooling rate of different school programs (gymnasiums, vocational and industrial schools). Questionnaires were filled by 478 8th grade pupils from primary, 551 1st grade pupils from secondary schools, by 595 teachers (327 from primary and 278 from secondary schools) and 596 parents (289 from primary and 307 from secondary schools). The response rate was 81% for primary schools and 78% for secondary χ schools.

The questions common for all respondents were: „Do you know the name of your school doctor/school doctor of my child/of my school"; "Do you know the address of the school health service (SHS)". Possible answers were „yes", no" and "not sure". Than the following statements were listed to all respondents: „The SHS office is available and accessible"; „Working hours are convenient"; „I do think that counselling in SHS is reasonable and useful"; „Physician is complaisant and willing to help/is responsible"; „Nurse is complaisant and willing to help/responsible". Pupils were asked whether confidentiality in SHS is respected and parents whether they turn to the SHS with confidence. Pupils were asked whether they attended check-ups regularly, and teachers and parents whether they obtained necessary information after check-ups. Parents and teachers were asked whether SHS could have been easily replaced by paediatricians or general practitioners and whether contacts with SHS were insufficient and ineffective. Teachers were asked whether SHS were necessary partners for schools. The possible answers ranged in the 5-point scale from „agree completely" to „disagree completely".

All groups were asked whether they sought help in specific areas from the SHS, and if yes, how they would rate the received help and support ranging from 1 to 5. The possible challenges were learning difficulties,

chronic diseases, nutrition and physical activity, reproductive health, injuries, behavioural problems, bullying, vocational counselling.

The results were presented in frequency tables. The significance was tested through Fisher's Exact Test and Independent sample t-test, using IBM SPSS22 statistics program.

RESULTS

The name of school doctor was best known to the primary school teachers (82.6%), and less known to the secondary school pupils (7.8%) (Table 1). Every fourth pupil from the primary as well as from the secondary school was not sure about the school doctor's name. Pupils from primary schools (both genders) rated higher than secondary school pupils the SHS availability, working hours' convenience and physicians' and nurses' complaisant and willing to help ($p<0.001$) (Table 2). Regarding counselling, confidentiality and health education lessons difference was not significant. More than 60% of pupils perceived counselling as useful and confidentiality respected. Health education lessons were found interesting by 45.0% pupils from primary and 41.7% pupils from secondary schools. Primary school pupils attended check-ups more regular than secondary school pupils ($p<0.001$). The lowest rating was for the working hours - 39.2% and 31.9%; $p<0.001$.

Analysed by the gender, males in primary school found SHS more available and working hours more convenient, but attended check-ups less regularly than females ($p<0.001$) (Table 3). In perception of the SHS staff's behaviour and attitudes and confidentiality in SHS were no significant gender differences. Usefulness of counselling in SHS and of health education lessons females rated higher than males (74.5 and 64.5; $p=0.01830$; 51.0 and 38.1; $p<0.001$). Gender differences

Table 1. Pupils, parents and teachers who know name of the school doctor

I know the name of the school doctor	Pupils primary schools N (%)	Pupils secondary schools N (%)	Teachers primary schools N (%)	Teacher secondary schools N (%)	Parents primary schools N (%)	Parents secondary schools N (%)
Yes	188 (39.4)	43 (7.8)	262 (82.6)	162 (58.0)	195 (67.5)	108 (35.2)
No	189 (39.5)	376 (68.2)	23 (7.3)	88 (31.7)	69 (23.9)	159 (51.8)
Not sure	101 (21.1)	132 (24.0)	32 (10.1)	28 (10.3)	25 (8.7)	40 (13.0)
Total	478 (100.0)	551 (100.0)	317 (100.0)	278 (100.0)	289 (110.0)	307 (100.0)

Table 2. Pupils from primary and secondary schools who agree/strongly agree on the SHS availability, staff behavior, check-ups attendance, counselling, confidentiality and health lessons

	Pupils primary schools Agree/strongly agree N (%)	Pupils secondary schools Agree/strongly agree N (%)	P
SHS available and accessible	286 (58.7)	190 (34.5)	<0.001
Working hours convenient	191 (39.2)	176 (31.9)	<0.001
Physician in SHS complaisant and willing to help	352 (73.3)	299 (54.3)	<0.001
Nurse in SHS complaisant and willing to help	341 (71.3)	298 (54.1)	<0.001
I attend check-ups regularly	434 (90.4)	430 (78.0)	<0.001
Counselling in SHS is reasonable and useful	334 (69.7)	362 (65.7)	0.16817
In SHS confidentiality is respected	326 (68.2)	342 (62.1)	0.03981
Health lessons held by SHS are useful and interesting	215 (45.0)	230 (41.7)	0.23069

Table 3. Pupils from primary schools, by gender who agree/strongly agree on the SHS availability, staff behaviour, check-ups attendance, counselling, confidentiality and health lessons

	Primary schools males Agree/strongly agree N (%)	Primary schools females Agree/strongly agree N (%)	P
SHS available and accessible	131 (58.7)	190 (34.5)	<0.001
Working hours convenient	191 (39.2)	176 (31.9)	<0.001
Physician in SHS complaisant and willing to help	158 (72.5)	190 (74.5)	0.61724
Nurse in SHS complaisant and willing to help	149 (68.7)	187 (73.6)	0.23553
I attend check-ups regularly	192 (84.2)	236 (92.5)	<0.001
Counselling in SHS is reasonable and useful	140 (64.5)	190 (74.5)	0.01830
In SHS confidentiality is respected	142 (65.4)	180 (70.9)	0.20669
Health lessons held by SHS are useful and interesting	82 (38.1)	130 (51.0)	<0.001

among pupils in secondary schools were less obvious (Table 4). Males found SHS more available (p<0.001), working hours more convenient (p=0.01128). Females attended check-ups more regularly (p=0.0294) and found counselling more useful (p=0.02370). Regarding SHS staff behaviour, health education lessons and confidentiality were no gender differences. Teachers from primary schools rated higher SHS availability, working hours' convenience, SHS staff behaviour and appropriate information after check-ups (p<0.0001) (Table 5). In perception of SHS as necessary partners for schools, for counselling and SHS participation in health education were no differences. Teachers were asked whether SHS could have been replaced by paediatricians or GPs and 35% and 33% answered positively, others did not approve of the suggestion; that contacts with SHS are insufficient and ineffective thought only 21% and 24.5%. SHS as necessary partners for schools perceived 88.9% teachers from primary and 82.3% form secondary schools (p=0.0231).

The greatest differences in SHS perception were found between parents from primary and secondary schools (Table 6). For all variables perception was more positive (p<0.001) by parents from primary school (SHS availability, working hours, staff behaviour, information after check-ups, counselling and health education usefulness and confidence in addressing SHS). That contact with SHS are insufficient and ineffective thought 28.2% parents from primary and 33.8% from secondary schools, and that SHS could have easily been replaced by paediatricians or GPs thought 21.7% parents from primary and 32.5% from secondary schools (p<0.001). Only for perception of the contacts with SHS was no difference (28.2% and 33.8% thought that contacts were insufficient and ineffective).

The questions all four groups were asked were presented in Table 7. The primary school teachers rated the SHS availability as the highest (71.2%), secondary school pupils the lowest (34.5%). Parents in primary schools rated the availability higher (68.5%) than parents in secondary schools (46.6%). Teachers and parents from primary school found the working time quite satisfactory, teachers and parents from secondary school rated convenience of working time lower. Pupils generally found the working hours not satisfactory enough. The physicians' complaisance and willing to help was perceived the highest by teachers, parents and pupils in primary schools (81.4%, 79.2% and 73.3%). A similar situation was with the perception of nurses, but parents and teachers from primary schools rated nurses even higher than physicians. That counselling in SHS is very useful agreed all groups of respondents - the highest

Table 4. Pupils from secondary schools, by gender who agree/strongly agree on the SHS availability, staff behaviour, check-ups attendance, counselling, confidentiality and health lessons

	Secondary schools males Agree/strongly agree N (%)	Secondary schools females Agree/strongly agree N (%)	P
SHS available and accessible	111 (40.4)	76 (29.2)	<0.001
Working hours convenient	103 (37.5)	71 (27.3)	0.01128
Physician in SHS complaisant and willing to help	140 (50.9)	143 (57.3)	0.34341
Nurse in SHS complaisant and willing to help	147 (53.5)	145 (55.8)	0.59096
I attend check-ups regularly	205 (74.6)	214 (82.3)	0.02943
Counselling in SHS is reasonable and useful	168 (61.1)	183 (70.4)	0.02370
In SHS confidentiality is respected	169 (61.5)	163 (62.7)	0.20669
Health lessons held by SHS are useful and interesting	110 (40.0)	112 (43.1)	<0.001

Table 5. Teachers from primary and secondary schools who agree/strongly agree on the SHS availability, staff behaviour, check-ups information, SHS as school partners, counselling, confidentiality and health lessons

	Teachers primary schools Agree/strongly agree N (%)	Teachers secondary schools Agree/strongly agree N (%)	P
SHS available and accessible	226 (71.2)	153 (55.1)	<0.001
Working hours convenient	207 (65.7)	123 (44.2)	<0.001
Physician in SHS complaisant and willing to help	258 (81.4)	182 (65.5)	<0.001
Nurse in SHS complaisant and willing to help	265 (83.6)	171 (61.5)	<0.001
I exchange necessary information after check-ups	236 (74.4)	133 (48.1)	<0.001
Contacts with SHS insufficient and ineffective	66 (21.0)	68 (24.5)	0.30648
SHS necessary partners for schools	280 (88.9)	229 (82.3)	0.02318
SHS could easily be replaced by pediatricians or GPs	35 (11.1)	33 (11.9)	0.77210
Counselling in SHS is reasonable and useful	281 (89.2)	239 (86.0)	0.23148
SHS participation in the health education reasonable and useful	285 (89.2)	240 (86.3)	0.24853

Table 6. Parents from primary and secondary schools who agree/strongly agree on the SHS availability, staff behaviour, check-ups information, contacts with SHS, counselling, confidentiality and health lessons

	Parents primary schools	Parents secondary schools	P
	Agree/strongly agree		
	N (%)	N (%)	
SHS available and accessible	195 (68.5)	142 (46.6)	<0.001
Working hours convenient	183 (63.5)	137 (45.2)	<0.001
Physician in SHS complaisant and responsible	229 (79.2)	162 (53.1)	<0.001
Nurse in SHS complaisant and responsible	234 (81.0)	157 (51.5)	<0.001
I obtain necessary information after check-ups	190 (66.2)	138 (45.2)	<0.001
Contacts with SHS insufficient and ineffective	80 (28.2)	103 (33.8)	0.13489
SHS could easily be replaced by pediatricians or GPs	63 (21.7)	99 (32.5)	<0.001
Counselling in SHS is reasonable and useful	237 (82.3)	202 (66.2)	<0.001
I address SHS with confidence	156 (54.7)	127 (41.6)	<0.001
SHS participation in the health education reasonable and useful	223 (76.9)	192 (63.0)	<0.001

Table 7. Pupils, teachers and parents from primary and secondary schools who agree/strongly agree on the SHS availability, staff behaviour, counselling and health education

	Pupils primary schools	Pupils secondary schools	Teachers primary schools	Teacher secondary schools	Parents primary schools	Parents secondary schools
	Agree/strongly agree					
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
SHS available and accessible	286 (58.7)	190 (34.5)	226 (71.2)	153 (55.1)	195 (68.5)	142 (46.6)
Working hours convenient	191 (39.2)	176 (31.9)	207 (65.7)	123 (44.2)	183 (63.5)	137 (45.2)
Physician in SHS complaisant and responsible	352 (73.3)	299 (54.3)	258 (81.4)	182 (65.5)	229 (79.2)	162 (53.1)
Nurse in SHS complaisant and responsible	341 (71.3)	298 (54.1)	265 (83.6)	171 (61.5)	234 (81.0)	157 (51.5)
Counselling in SHS reasonable and useful	334 (69.7)	362 (65.7)	281 (89.2)	239 (86.0)	237 (82.3)	202 (66.2)
SHS participation in the health education useful/interesting	215 (45.0)	230 (41.7)	285 (89.2)	240 (86.3)	223 (76.9)	192 (63.0)

rating by teachers from primary schools (89.2%). The greatest disparity occurred regarding the perception of SHS participation in health education. Teachers and parents assessed the SHS participation in health education reasonable and useful, and only 45.0% pupils from primary and 41.7% from secondary schools found health lessons held by SHS interesting.

When asked about common reasons for contacting SHS beyond regular group activities, the greatest percentage of pupils from primary schools contacted SHS for vocational counselling (39.2%), for secondary school pupils the most common reason were chronic diseases (52.6%) (Table 8). Teachers in primary schools found the most important reasons for SHS help learning difficulties (62.1%), teachers from secondary schools sexual and reproductive health 45.9%. Parents from primary schools asked help and advice most often for vocational counselling (27.5%), and parents from secondary schools for chronic diseases (15.2%).

The respondents rated their satisfaction with the services regarding the most common issues at the five-point scale (Table 9). The satisfaction among primary school pupils was the highest for vocational counselling (4.1), injuries (3.8) and then nutrition and sexual health (3.7); for secondary school pupils for injuries (3.8), sexual and reproductive health and behavioural problems (3.6). There was no difference between ratings measured by t-test. Teachers from primary schools rated the highest chronic diseases (4.1), nutrition and injuries (4.0), teachers from secondary schools were mostly satisfied with the help regarding sexual health (4), chronic diseases and nutrition (3.6). The difference was found for most issues, teachers from secondary schools being less satisfied for learning difficulties, chronic diseases, bullying and vocational counselling ($p<0.001$) and for nutrition, injuries and behavioural problems ($p<0.005$). Parents from primary schools rated care for chronically ill children as the highest (4.0), being more satisfied with solving learning difficulties, behavioural problems and vocational counselling ($p<0.001$) than parents from secondary schools.

Table 8. Pupils, parents and teachers from primary and secondary schools who used SHS for common adolescents' problems

	Pupils primary schools N (%)	Pupils secondary schools N (%)	Teachers primary schools N (%)	Teacher secondary schools N (%)	Parents primary schools N (%)	Parents secondary schools N (%)
Learning difficulties	89 (18.3)	268 (48.6)	194 (62.1)	70 (24.7)	56 (19.5)	46 (14.8)
Chronic diseases	94 (19.3)	290 (52.6)	184 (59)	107 (37.8)	67 (23.3)	47 (15.2)
Nutrition and physical activity	136 (27.9)	230 (41.7)	182 (58.3)	105 (37.1)	54 (18.8)	41 (13.3)
Sexual and reproductive health	121 (24.8)	235 (42.6)	188 (60.3)	130 (45.9)	53 (17.8)	44 (14.2)
Healthy lifestyle	150 (30.8)	220 (39.9)				
Getting certificates	133 (27.3)	238 (43.2)				
Injuries	159 (32.6)	229 (41.6)	167 (53.5)	84 (33.2)	63 (22)	47 (15.2)
Behavioural problems	90 (18.5)	216 (39.2)	188 (60.3)	96 (33.9)	46 (16.2)	37 (12)
Bullying and violence	95 (19.5)	205 (37.2)	160 (51.3)	79 (27.9)	45 (15.6)	35 (11.3)
Vocational counselling	191 (39.2)		179 (57.3)	72 (25.9)	79 (27.5)	46 (14.8)

Table 9. Satisfaction of pupils, parents and teachers from primary and secondary schools with the SHS response to the common adolescents' problems (scale 1-5)

	Pupils primary schools	Pupils secondary schools	Teachers primary schools	Teacher secondary schools	Parents primary schools	Parents secondary schools
Learning difficulties	3.2	3.2	3.8**	2.7**	3.9**	2.5**
Chronic diseases	3.1	3.0	4.1**	3.6**	4.0	3.6
Nutrition and physical activity	3.7	3.5	4.0*	3.6*	3.6	3.1
Sexual and reproductive health	3.7	3.6	4.1	4.0	3.8	3.1
Injuries	4.0	3.8	4.0*	3.5*	3.9	3.4
Behavioural problems	3.4	3.6	3.7*	3.1*	3.7*	2.7*
Bullying and violence	3.5	3.4	3.6**	2.7**	3.4	2.8
Vocational counselling	4.1		3.9**	2.7**	4.1**	3.1**

** $p<0.001$ * $p<0.005$

DISCUSSION

Among young people, health should be considered in its widest sense, in line with the WHO definition of health as not merely the absence of disease, but a state of complete physical, psychological, and social well-being (EU 2009). That means that it is necessary to make health-service youth friendly and to ensure that the health services for young people are being provided in the right manner. To be considered adolescent friendly, health services should be accessible, acceptable, equitable, appropriate and effective (WHO 2012). For the provision of the services in the line with this recommendation, at the national level is necessary to have legislation framework and organizational structure (Kuzman, Hoppenbrouwers, Juricic 2008). There are great variations in organization, structure, content and staff in SHS in European countries (Wieske et al. 2012). In some countries (Finland, Slovenia, Macedonia, Norway, Great Britain) the school health services are responsible for the comprehensive health care for schoolchildren and university students, providing preventive and curative care as well. If SHS are oriented toward the preventive activities only, it is necessary to have defined content and program. According to the survey results among 11 European countries, in Belgium, Netherlands, Germany, Croatia, Switzerland and Hungary the activities are undertaken according to the annual program and are mainly focused to the preventive measures.

The existing school health services in Europe employ a wide range of professionals - medical doctors, nurses, psychologists, social workers. The common characteristic of the majority of countries is that for being fully engaged in these services, medical doctors have to have specific education, consisting of post-graduate study or special competences training, sub-specialization in school medicine or independent specialization in school and adolescent medicine (Hoppenbrouwers et al. 2007). WHO together with EUSUHM (European Union for School and University Health and Medicine) developed a European framework for quality standards in SHS and competences for school health professionals (WHO 2014).

The core set of competences reflects seven roles of the CanMEDS model developed by the Royal College of Physicians and Surgeons in Canada (RCPSC 2005, WHO 2014). According to the document, SHS expert needs to act as SHS expert, professional, communicator, collaborator, manager, health advocate and scholar.

The satisfaction with SHS is very difficult to compare between countries due to thegreat diversity of the organization and services delivered. According to the results of our survey, the differences of the perception exist between pupils, parents and teachers from primary and from secondary schools. In primary schools all groups of respondents found accessibility higher, working hours more convenient, SHS staff more complaisant and willing to help. The SHS accessibility and availability in Croatia should have been generally very high, as for the each school medical staff consisting of the school doctor and nurse is appointed. But the contacts with schools, school staff, parents and pupils are more frequent in primary than in secondary schools, so the perception of the availability is understandably higher.

Working hours also contribute to the perception of the accessibility. Although SHS work from morning till evening alternating mornings and afternoons in shifts (every second day), satisfaction with the working hours was rather low. Majority of Croatian parents work through the morning, and it might be that the reason for the low perception. It is interesting that pupils in secondary school were less satisfied with the working hours. The possible explanation could be that pupils in secondary schools should travel to the school and SHS is basically not always located near the school itself, so for some of them to visit SHS was not convenient during working days. The SHS staff behaviour was rated by teachers as very high (from primary and secondary schools as well). Teachers according to the results, clearly recognized SHS as welcomed partners in the necessary care for school children. They rated the communication a very good, information exchange as satisfactory and only every fifth of them considered contacts with SHS as insufficient and ineffective.

In the systems where SHS are represented by school nurses (i.e. US, Great Britain), research showed that school system collaboration issues need more school nurse involvement (Winland & Shannon 2004). It was stated that school nurses need to improve their visibility regarding school system collaboration, and in the classroom and individual pupil education. Results indicated that staff would be more satisfied if they had more nursing support in the classroom and more nurse time in their building. In a way it supports our results (regardless the professionals involved), because in primary schools where contacts are more frequent and activities more intensive, perception was higher and more positive. Although SHS in Croatia underwent organizational changes and provide preventive care only, when asked about the possibility of replacing them with paediatricians or GP offices, teachers and parents were against the idea. When comparing the answers, the least positive responses were from teachers from primary schools and the vague answers were from parents from secondary schools.

One of the reasons for SHS less favourable perception from pupils and parents from secondary school could be the time of the survey. The survey was done at the beginning of the spring semester, meaning that in many first year classes in secondary schools regular check-ups have not been done yet, so many pupils had not met SHS staff. Assessing some of the activities the majority of pupils and grown-ups were in favour of the SHS counselling. Counselling in SHS is aiming at risk behaviour, healthy lifestyle, but also at learning difficulties and mental health problems. It is encouraging that counselling is recognized as useful and needed activity. Physicians should specifically target these risk factors with preventive counselling, although adolescents may be reluctant to initiate discussions about risky behaviours because of confidentiality concerns. The key to providing relevant and useful preventive counselling for adolescent patients is developing the trust necessary to discuss the specific issues that impact this age group (General Medical Council 2007).

It is interesting to observe the difference among the respondents' groups about health education. Health education has been provided by SHS staff for several decades already, and since 2012 became part of the regular curriculum. There is evidence to suggest that sexuality education is most effective when based on curriculum-based programs and comprehensive life skills-based approaches. Further efforts to ensure that such programs are available and that their development, content and implementation follow internationally agreed standards based on best practices are likely to produce benefits (Patrick 2011). When perception among pupils was analysed, the gender differences were found. Females in primary and secondary schools found SHS less available and health education lessons more interesting. As health education embraces sexuality education among other issues, it might be that girls were more interested in the themes. Health behaviours and patterns of access to health services among adolescents and young people tend to follow clearly identified gender-specific determinants. Policies targeting adolescents and young people that reflect these gender-specific determinants, and which are informed by sex-disaggregated data, are likely to be more effective (Patrick 2011).

It is encouraging that pupils consider confidentiality in SHS as being respected. Confidentiality in adolescent counselling is very much discussed issue (Society for Adolescent Medicine 2004, English&Ford 2007). The concerns about confidentiality could be at least one of the reasons for not trying to obtain help when needed (Akinbami et al. 2003, Lehrer et al. 2007). However, health providers have to be flexible, because blind adherence to absolute confidentiality or absence of confidentiality is neither desirable nor required by ethic or law. It is therefore important that parents stated their confidence in SHS, because it reflected their belief that the staff will act in the best interest of a young person taking into account context and possible consequences.

The involvement in different health issues differs substantially in other surveys too, as it depends on the

health status, circumstances, staff competencies and environment. The reasons for addressing SHS reflect the common problems adolescents and their parents are facing through this period of life (WHO/UNFPA/ UNICEF 1999). As SHS in Croatia work closely with the school staff, learning difficulties were among most regular reasons for seeking help. The age of the respondents could have influenced the answers, as it seems that for parents and pupils from primary schools learning difficulties have been mostly solved, but for teachers from primary schools it still has been important issue. The same applied to chronic disease problems, by the end of primary schools all important activities regarding chronically ill children have already been undertaken and especially pupils did not find it very important. It is obvious that healthy lifestyle, nutrition and physical activity became important for pupils and parents, which reflects the growing number of overweight children and consequent population concern (Kuzman 2009, Kuzman Pavic Simetin, Pejnovic Franelic 2011). The overweight problem among children and youth indicates that risk factors for high BMI as physical inactivity and unhealthy diet are not the only important issues. Adolescents' self-perception is not in accordance to the actual weight and height, and that makes them vulnerable regarding self-esteem as well as life satisfaction assessment.

Youth-friendly sexual and reproductive health services are those that attract young people, respond to their needs, and retain young clients for continuing care Juntunen 2004). The activities are based on a comprehensive understanding of what young people in a given society or community want, and with respect for the realities of their diverse sexual and reproductive lives. The aim is to provide all young people with services they trust and which they feel are intended for them. Following the recommendation form comprehensive survey done through UNICEF initiative, within SHS in the City of Zagreb additional specialized counselling on sexual and reproductive health was organized. The responses from teachers and pupils reflected that these activities were accepted and used.

Behavioural problems are not rare through schooling years, but the beginning of secondary schooling could be very vulnerable period of adolescent life (Graovac et.al 2006). The changes of the school environment, classroom peers, necessity to change neighbourhood, sometimes to leave home – all this might be reflected in behavioural problems. Therefore, it is not uncommon that these problems were listed more in secondary than in primary schools.

Bullying is not an isolated event in the school classrooms and schoolyards. The complexity of this behaviour is indicated by the evidence that among children involved in bullying psychosomatic symptoms and poor family communication are more often registered. SHS are actively involved in solving problems connected to bullying and again teachers rated high their involvement (Kuzman, Pavic Simetin, Pejnovic Franelic 2011).

CONCLUSIONS

Perception of the SHS in the City of Zagreb differs from different population groups. Teachers from primary schools rated SHS in different aspects of the care as the highest and in secondary schools, assessed by pupils and parents, the perception was lower. Limitations of the study were just two generations of pupils asked to provide reflection and opinions, but this was done for practical reasons and in attempts to prove the distinction between primary and secondary schools. It would be useful to study more in depth the reasons for such change in perception among pupils, taking place just in one school year. Nevertheless, SHS as specific services for children and youth have advantages. Existing SHS network reaches not only cities and towns, but the most remote areas of Croatia, ensuring that each student and school have a school doctor. A defined program of preventive activities, financed by Compulsory Health Insurance provide the harmonized care for school children and adolescents, in line with professional recommendations. SHS are organized on the primary health care level, so pupils have direct approach to service. The close collaboration with schools proves that school is considered as a setting where children are easily available for health interventions, where is easy to follow the epidemiological situation and where health education programs might be successfully implemented. Confidentiality is respected and counselling ensure individual approach, in addition to the group activities undertaken in the school. SHS proved to be of a great help and support for school staff, but less for parents and quite low for secondary school pupils.

Common reasons for asking help from SHS prove that the intervention from their side is needed. Therefore, the model of comprehensive health care or at least more possibilities for intervention would provide an easier solution for pupils and parents improving possible impact on perception of the services by the population.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 485-489 *Original paper*

SMOKING BEHAVIORS AND LUNG CANCER EPIDEMIOLOGY: A COHORT STUDY

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SUMMARY

Background: *Lung cancer is the most common cancer in the world. According to the latest available data, in the year 2012 Croatia was among 20 countries with the highest incidence of lung cancer. Although tobacco smoking is a proven cause of lung cancer, recent data show that more than one quarter of adult inhabitants of Croatia are everyday smokers. The purpose of this study was to present epidemiology and treatment modalities of lung cancer in the Department for mediastinal tumors, Clinic for lung diseases Jordanovac, and to make a comparison between the available data from Croatia and the rest of the world.*

Subjects and methods: *The study cohort included 212 newly diagnosed lung cancer patients who had referred to our Department from January 2012 until December 2012. Features such as age, gender, cytology and histology of the tumor, stage at diagnosis and applied therapy were evaluated respectively.*

Results: *Approximately two-thirds of all newly diagnosed lung cancers occurred in men. Out of the study cohort, 12.3% were diagnosed with small cell lung cancer (SCLC) and 87.7% were diagnosed with non-small cell lung cancer (NSCLC). The majority of the patients diagnosed with NSCLC had adenocarcinoma (47.9%), followed by squamous cell carcinoma (33.9%) and large cell carcinoma (15%). Only a small number of patients diagnosed and treated for lung cancer in our Department had never smoked tobacco. The majority of those patients were women and the most common histological type found was adenocarcinoma.*

Conclusion: *The number of patients who had potentially operable disease at presentation was around 10%. That is why, in most cases, therapeutic options were confined to palliative chemotherapy or radiotherapy. Attention should be directed to an early detection of lung cancer patients, which could provide better treatment options and improve overall survival.*

Key words: *lung cancer - lung cancer epidemiology - tobacco smoking - lung cancer treatment*

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INTRODUCTION

Lung cancer is the most common cancer in the world. In the year 2012 there were 1.8 million new cases diagnosed (Ferlay 2012). The same year, Croatia was among 20 countries with the highest incidence of lung cancer, with the world age-standardized rates as high as 34.3 per 100,000 persons (Ferlay 2012). There was an increase compared to the year 2011, when the world age-standardized rate was 33.3 per 100,000 persons. According to the latest data available from the Croatian National Cancer Registry, in the year 2011 in Croatia, lung cancer was the most common solid tumor in men with the incidence rate of 104.1/100,000 persons and the second most common tumor in women with the incidence rate of 34.6/100,000 persons (Croatian National Cancer Registry 2013). Tobacco smoking and exposure to environmental tobacco smoke is a proven cause of lung cancer (Hackshaw et al. 1997, Vineis et al. 2004, IARC 2004), responsible for the development of approximately 85% to 90% of all lung cancers (National Comprehensive Cancer Network 2014). Recent data show that more than one quarter of adult inhabitants of Croatia are everyday smokers, which presents a great public health problem (Kovačić et al. 2007, Samardžić et al. 2009). Approximately 95% of all lung cancers are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). There are three main subtypes of NSCLC, including squamous cell carcinoma accounting for about 25% of all lung cancers, adenocarcinoma accounting for about 40%, and large cell carcinoma for about 10% of all lung cancers. About 10% to 15% of all lung cancers are small cell lung cancers. The distribution of NSCLC subtypes is changing. In the last 30 years the incidence of squamous cell carcinoma has been declining while adenocarcinoma has become more frequent (Devesa et al. 2005). The majority of patients present with locally advanced or metastatic disease at the time of diagnosis (stage IIIb or stage IV). Survival rates vary depending on the stage at diagnosis. The median survival time for patients with untreated metastatic NSCLC is 4 to 5 months, with a survival rate at one year of only 10% (Rapp & Pater 1988). Chemotherapy combinations showed a response rate of 19–32% and a median survival time of 7.9 to 11.3 months (Schiller & Harrington. 2002, Fossella & Pereira 2003, Čučević et al. 2005).

The purpose of this study was to present epidemiology and treatment modalities of lung cancer in the Department for mediastinal tumors, Clinic for lung diseases Jordanovac, and to make a comparison between the available data from Croatia and the rest of the world.

SUBJECTS AND METHODS

The study cohort included all newly diagnosed lung cancer patients who had referred to the Department for mediastinal tumors, Clinic for lung diseases Jordanovac, University Hospital Center Zagreb, from January 2012 until December 2012. In the observed period there were 212 patients diagnosed and treated for lung cancer. Features such as age, gender, cytology and histology of the tumor, stage at diagnosis and applied therapy were evaluated respectively. Cytology and histology data were analyzed according to the World Health Organization (WHO) histological classification (Table 1).

Table 1. Patinents and tumor characteristics

Characteristic	N	Percentage
Gender		
Male	153	72.2
Female	59	27.8
Age	65; 37-85	
Histology		
NSCLC	186	87.7
SCLC	26	12.3
NSCLC		
Adenocarcinoma	89	47.9
Squamous cell	63	33.9
Large cell	28	15.0
Other types	6	3.2
Tobacco users		
Smokers	182	85.8
Non-smokers	30	14.2

N – number of patients; NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer

Radiologic methods used to assess the disease were contrast-enhanced computed tomography scan of chest and upper abdomen, positron emission tomography for evaluation of preoperative treatment, brain imaging and bone scan for clinical suspicion of metastatic disease. Tumor staging was recorded according to the current seventh edition of tumor node metastasis (TNM) classification by The International Association for the Study of Lung cancer (IASLC) (Table 2). Treatment was carried out according to the latest National Guidelines. The first line of treatment for NSCLC stage I, II, and IIIA was surgery (lobectomy, or pulmectomy and lymph node dissection) alone or followed by chemotherapy. The patients who were not willing to accept the procedure-related risk or could not undergo surgery due to co-morbidities, received radio and chemotherapy. Treatment of locally advanced or metastatic disease was based on cisplatina regimens delivered alone or concurrently with radiotherapy. The patients who were not fit for concurrent treatment received chemotherapy alone or with radiotherapy in non-concurrent schedule (Pignon & Stewart 1996). In metastatic or locally advanced disease, platinum was combined with gemcitabine, taxanes and etoposide as the first line chemotherapy (Schiller et al. 2002, Ardizzoni et al. 2007). The patients who had clinical or radiological progression during or after the first line of treatment, received, when possible, pemetrexed or docetaksel as mono-therapy (Di Maio et al. 2009, Hanna et al. 2004). Erlotinib was applied as mono-therapy (Shepherd et al. 2005), when possible, to the patients who had radiological proof of progression on the second line of treatment. The collected data were correlated with Department data from the year 2011 and the available literature data.

Table 2. TNM classification

Staging	N	Percentage
Ia	2	0.9
Ib	3	1.4
IIa	2	0.9
IIb	4	1.9
IIIa	13	6.2
IIIb	31	14.6
IV	157	74.1
All stages	212	100.0

N – number of patients

RESULTS

Out of 212 patients with lung cancer, 153 were male (72.2%) and 59 female (27.8%). The mean age at the time of diagnosis was 65 years, ranging from 37 to 85 years. Out of all the newly diagnosed patients, 26 of them (12.3%) were diagnosed with SCLC and 186 of them (87.7%) were diagnosed with NSCLC. The majority of the patients diagnosed with NSCLC had adenocarcinoma (47.9%), followed by squamous cell carcinoma (33.9%), and large cell carcinoma (15%). Other subtypes were found in 3.2% of the cases. A significant number of the patients (182 of them, 85.8%) were former or active smokers. In the group of the patients who were non-smokers, most of them were diagnosed with adenocarcinoma (22 patients, 73.3%), while the others had squamous cell carcinoma (3 patients, 10%), small cell carcinoma (3 of them, 10%) and large cell carcinoma (2 patients, 6.4%). The majority of the patients in the non-smoking group were women (70%). Only 24 patients (11.3%) were diagnosed with potentially operable disease, all of which had NSCLC, while 188 patients (88.7%) had an advanced stage of disease (IIIB, IV) at the time of diagnosis. Out of the potentially operable patients, 22 (10.4%) were sent to a curative operation procedure (Table 3). Altogether 91 patients (42.9%) had brain or bone metastases, or a locally advanced tumor and received radiotherapy at some point during the treatment (Table 4). Out of all the study population, 159 patients (75%) received some type of chemotherapeutic regimen. As many as 53 patients did not receive chemotherapy due to bad ECOG performance status, co-morbidity or refusal of further treatment. In the SCLC group, 21 patients received platinum-based doublet with etoposide in the first line of

Table 3. Surgical treatment of NSCLC

Stage of disease	N	Neo-adjuvant chemotherapy	Adjuvant chemotherapy	Lob/pulm with LND
Ia	2	/	/	2
Ib	3	/	1	3
IIa	2	/	2	2
IIb	4	1	3	4
IIIa	13	8	11	11

N – number of patients; Lob/pulm – lobectomy/pulmectomy; LND – mediastinal limph node dissection

Table 4. Radiotherapeutic regime

Location	N	Percentage
CNS	34	37.4
Gamma-knife	6	
WBRT	28	
Lung and mediastinum	31	34.1
Concurrent C/R	15	
Non-concurrent C/R	16	
Bones	26	28.5

N – number of patients; CNS – central nervus system; WBRT – Whole brain radiotherapy; C/R – chemotherapy/radiotherapy

Table 5. Therapeutic regime for SCLC

Therapeutic regime	LoT	Chemotherapeutic option	N.C.	N	Percentage
Operation				/	
BSC				5	19.2
RT				13	50.0
Chemotherapy	First	PE	3.8	21	80.8
	Second			13	50.0
		Topotecan	3	5	19.2
		PE	2.7	7	26.9

N – number of patients; LoT – line of treatment; BSC – best supportive care; N.C. –average number of cycles; RT- radiotherapy; PE – cisplatinum or carboplatinum plus etoposide

Table 6. Therapeutic regime of NSCLC

Therapeutic regime	LoT	Chemotherapeutic option	N.C.	N	Percentage
Operation		Neo-adjuvant and/or adjuvant		22	11.8
BSC				31	16.7
RT				78	41.9
Chemotherapy	First			138	74.2
		PE	3.6	60	
		GC	3.7	31	
		Taxol/C	3.6	47	
	Second			56	30.0
		PE	2.9	8	
		GC	4.2	5	
		Pemetrexed	2.5	20	
		Docetaxel	2.8	18	
		Taxol/C	3.6	5	
	Third			31	16.7
		PE	3.5	2	
		Erlotinib	6.3	29	

N – number of patients; LoT – line of treatment; BSC – best supportive care; N.C. –average number of cycles; RT- radiotherapy; PE – cisplatinum or carboplatinum plus etoposid; GC – cisplatinum or carboplatinum + gemcitabine; Taxol/C – cisplatinum or carboplatinum + paclitaksel

chemotherapy and 13 patients received radiotherapy. After registered radiological progression, 13 patients were fit to receive the second line chemotherapy, which included either platinum based regiment or topotecan as mono-therapy (Table 5). In the NSCLC group, 138 patients (74.2%) received chemotherapy and 78 patients (41.9%) received radiotherapy. All the patients in the NSCLC group received platinum-based chemotherapy doublets in the first line of treatment. Carboplatinum or cisplatinum were combined with etoposide (43.5%), gemcitabin (22.5%), or paclitaxel (34%). Out of the patients who had progression during or after the first line, 30% were able to receive the second line of treatment. The majority of the patients (35.6%) received pemetrexed as mono-therapy in the second line of treatment, followed by different types of platinum-based doublets (32.2% patients), or docetaxel as mono-therapy (32.2% patients). Only 16.7% of the patients received the third line of treatment due to further progression; 93.5% of them received erlotonib and only 6.5% received platinum with etoposide (Table 6).

DISCUSSION

The data collected in this study show that approximately two-thirds of all newly diagnosed lung cancers occurred in men. A similar ratio of the incidence of lung cancer in men and women was observed in the year 2011 in our Department (72% men, 28% women). This is in concordance with the data from the Croatian National Cancer Registry for the year 2011, according to which, out of 2,920 newly diagnosed lung cancer patients, 2,152 (73.7%) were men. In comparison with the data of the previous years in Croatia, the incidence of lung cancer in men fluctuates around the same value and the incidence in women is increasing. Using the world age standardized rates (ASR) for lung cancer incidence, cancer rates for lung cancer in Croatian men are still three times higher than in women, while in developed countries the rate difference is significantly lower (developed countries ASR for men 44.7, for women 19.6/Croatia ASR for men 58.2, for women 15.4). Based on the GLOBOCAN 2008 (developed countries ASR for men 47.4, for women 18.6), it seems that in developed countries the incidence of lung cancer in men decreased while the incidence in women slightly increased. A plausible explanation for this could be found in fierce anti-smoking campaigns that reduce the number of active smokers in developed countries. The situation in Croatia is troubling because there is no overall decline in the number of smokers and the number of women who smoke is growing. Analyses show that only a small number of patients diagnosed and treated for lung cancer in our department have never smoked tobacco. In accordance with the previous findings, the majority of those patients were women and the most common histological type found was adenocarcinoma (Couraud et al. 2012).

The number of newly diagnosed patients admitted to our Department in 2012, who had potentially operable disease at presentation, was around 10%. That is why, in most cases, therapeutic options were confined to palliative chemo or radiotherapy. Current data estimate the number of patients with potentially operable, early stage disease at initial diagnoses to be around 20-30% of all newly diagnosed lung cancer patients (Mauguen et al. 2013, Ellise & Vandermeer 2011, Little et al. 2005). Survival rates vary depending on the stage of the disease, emphasizing the need for an early diagnosis. Current National Comprehensive Cancer Network (NCCN) Guidelines recommend annual lung cancer screening with low dose computed tomography (LDCT) for individuals with the following risk factors: age 55 to 74 years, 30 or more pack year history of smoking tobacco, and current smokers or, if former smokers, have quit within 15 years. For now there is no National Screening Program for lung cancer in Croatia. The distribution of histological types was almost the same as in the year 2011.

Chemotherapeutic treatment was applied in accordance with the latest guidelines whenever it was feasible. Due to the poor general condition at the time of diagnosis, a lot of patients could not receive recommended treatment protocols. Only a handful of patients were able to receive the third line of chemotherapy. Previous studies showed that an early initiation of targeted therapy in the designated patients improves their outcome. European Society for Medical Oncology (ESMO) has already included the prescription of TKIs as the first line treatment to patients with tumors bearing an activating EGFR mutation (Peters et al. 2012). The question of an early detection of patients who are carriers of the epidermal growth factor receptor (EGFR) mutations, proper to receive tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib as the first or second line of chemotherapy, should be considered.

CONCLUSION

Lung cancer is still one of the leading causes of cancer morbidity and mortality in Croatia. Additional efforts should be made to prevent cancer-causing behavior such as smoking tobacco. Attention should be directed to an early detection of lung cancer patients, which could provide better treatment options and improve overall survival.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 490-497 *Original paper*

OROFACIAL INJURIES REPORTED BY PROFESSIONAL AND NON-PROFESSIONAL BASKETBALL PLAYERS IN ZAGREB AND ZAGREB COUNTY

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SUMMARY

Background: *Injuries are common during sport activities, a part of which is also injuries to the stomatognathic system. According to the data from literature orofacial injuries are frequent, but relatively minor. World Dental Federation has listed basketball as a medium-risk sport in sustaining orofacial injuries. The purpose of this investigation was to determine incidence, type and severity of orofacial injuries during basketball and frequents of mouthguard use.*

Subject and methods: *The sample consisted of 195 athletes who actively participate in basketball, 60 amateurs/non-professional and 135 professionals.*

Results: *A total of 2 265 injuries to the stomatognathic system were documented in this research; 200 (8.8%) of those injuries refer to the non-professionals and 2 065 (91.2%) to the professionals. The most common injuries are lacerations and contusions of soft tissue (a total of 2 208 or 97.5%), followed by dental injuries (a total of 57 or 2.5%). Out of all recorded laceration injuries 59.8% lacerations of soft tissue occurred during practice (12.6% amateurs and 87.4% professionals), while 40.2% of them occurred during games (2.5% amateurs and 97.5% professionals). Of a total of 57 dental injuries recorded during an athletes career, in 78.9% it were the professionals who suffered an injury, and in 21.1% of them the amateurs. Out of a total of 195 basketball players only 1% (2 players - one professional and one amateur) frequently used mouthguard during practice and games, while 93.3% of them never tried to wear a mouthguard. Such low percentage of mouthguard use in basketball players reflects poor awareness and education of athletes and coaches, as well as insufficient role of dentists in education.*

Conclusions: *Orofacial injuries during basketball are not severe (80% lacerations), and therefore do not stimulate the use of a protecting devices even their use will totally diminish this type of injuries.*

Key words: *orofacial injuries - basketball players – professional - amateurs/non-professional*

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INTRODUCTION

Based on continuous research many authors have come to the conclusion that the increased popularity of sports and exercising, apart from being beneficial to developing healthy habits, also results in a larger number of injuries (Torg et al. 1985, Powell et al. 1987, Helmrich et al. 1991, Sarna et al. 1993, Fentem et al. 1994, Kujala et al. 1994). The increased risk of sports-related injuries also results from an increase in the number of people participating in sports (Williams et al. 1998). Every sport is associated with its own specific injuries (Kujala et al. 1995), which includes injuries to the stomatognathic system (Jerolimov & Jagger 1997, Jerolimov & Carek 1997, Jerolimov & Seifert 1999). As early as in 1951, Cathcart (Cathcart 1951) described the necessity of protecting the stomatognathic system, not only during boxing or in American football, but also in other contact sports, such as: ice hockey, basketball and car racing. In the 1960s Moon and Mitchell (Moon & Mitchell 1961) stated that 10% of athletes in contact sports injured their stomatognathic system during just one season, while such injuries occurred in 33% to 56% of these athletes over the course of their entire career (Clegg 1969). Chapman (Chapman 1986), Braham et al. (Braham et al. 1997), Harmer (Harmer 2005) as well as dos Santos and Monte Alto (dos Santos & Monte Alto 2006) confirm this claim, emphasizing the possibility for prevention by wearing custom-made mouthguards. In 2003 Corwell et al. (Corwell et al. 2003) proposed that similar injury evaluations and the role of mouth-guards are extremely important in the development and implementation of guidelines for using protective equip-ment in basketball. Kumamoto and Maeda (Kumamoto & Maeda 2005) proposed that introducing mouthguard programs for athletes of all ages and genders who participate in basketball might help to reduce the incidence of dental trauma. Yeşil Duymuş and Gungor observed that in Turkey the use of mouthguards is rare, therefore it should be the joint duty of dentists, sports physicians, and coaches to encourage the use of mouth-guards during training and sport activities. Doctors and dentists need to recommend a more intensive education of students in sports medicine and sports dentistry (Yeşil Duymus & Gungor 2009).

Basketball is considered to be one of the most dynamic sports considering intensity throughout the entire forty minutes of the game, so basketball players need to possess a wide range of basic and specific functional and physical skills. Playing the game requires explosive strength, coordination in the execution of specific physical tasks, spatial orientation, agility in efficient dealing with new situations, the speed of the neuromuscular reaction and the speed of the movements

themselves (http://www.inet.hr/~ivdzolic, Matković & Matković 1996). Basketball is played on a relatively small court with constant contact among the players. Frequent contacts in the heat of the game often result in both intentional and unintentional injuries (Grujić et al. 1989). According to Whiteside, Zaricnyj et al. and Zelisko et al. (Whiteside 1980, Zaricznyj et al. 1980, Zelisko et al. 1982) the incidence of head, neck and orofacial injuries in basketball players varies from 10.3% to 12.7%. The FDI World Dental Federation places basketball into the category of medium-risk sports as far as the incidence of injuries to the stomatognathic system is concerned (FDI 1990). Contrary to the position of the FDI World Dental Federation, Morrow and Kuebker (Morrow & Kuebker 1986) have established that the incidence of injuries to the stomatognathic system is greater in basketball and soccer than in American football, which is, according to the FDI, a high-risk sport. In another research Newsome and associates (Newsome et al. 2001) demonstrate that dental injuries do not occur only in contact sports, such as rugby and hockey, but also in sports that may at first seem less dangerous, such as basketball. Garon et al. (Garon et al. 1986) point out that a large number of injuries to the stomatognathic system as well as a large number of concussions occur during baseball, basketball and amateur American football games, whereby they also state that 52% of injuries to the stomatognathic system result from taking part in some other sport, besides American football. Many authors (Backx et al. 1989, McLain & Reynolds 1989, Chan et al. 1993, Teo et al. 1995, Love et al. 1998, Stevenson et al. 2000) have compared injuries to the stomatognathic system in basketball with injuries in other sports and have noticed that the incidence of injuries is greater in basketball than in other sports. Their conclusion is further elaborated by McNutt et al. (McNutt et al. 1989) who have collected data on sports-related injuries over the course of three years and have subsequently matched the injuries to the stomatognathic system with different kinds of sports. They state that 40% of injuries refer to dental injuries of athletes practicing basketball and baseball, sports where there is no mandatory use of mouthguards. This is supported in research by Lee-Knight et al. (Lee-Knight et al. 1992) who recorded the largest percentage of injuries to the stomatognathic system during the Canada Games in wrestlers and basketball players, as well as in female athletes participating in basketball and field hockey. None of the athletes who injured their stomatognathic system during the competition wore a mouthguard. The analysis of sports-related injuries shows that in 51% of the cases, the responsibility for the injury rests with the athlete. This is mostly the result of carelessness, fatigue, bad physical shape or poor technique.

Someone else, an opposite team player, intentionally or unintentionally causes an injury in 28% of all cases. These are mostly severe knee injuries, bone fractures or head injuries. Other causes, such as equipment, field conditions, footwear, clothes and others will result in an injury in 21% of the cases (Grujić et al. 1989).

There is insufficient data on the injuries to the stomatognathic system in the Republic of Croatia, which is why the purpose of the research is to establish the representation and the severity of the injuries to the stomatognathic system in a selected sample of basketball players from the City of Zagreb and Zagreb County.

SUBJECTS AND METHODS

The sample consists of 195 athletes who actively participate in A1 and A2 basketball league in Croatia, including members of the National Basketball Team, as well as basketball amateurs/non-professionals. All of the athletes are male, aged between 16 and 49 years and all of them come from the City of Zagreb or Zagreb County. Before a questionnaire survey was conducted, the athletes were given instruction and direction for the purpose of the survey. The athletes filled out the questionnaire in person, with the help of a researcher. All of the questioned athletes were placed into categories of amateurs and professionals. In total, 60 amateurs and 135 professionals were interviewed (Table 1). Amateurs and professionals do not differ in terms of age in a statistically significant manner; the amateurs are in average 20.3 years old, whereas the professionals are 21.3 years old. Also, the average number of years spent actively playing basketball does not differ significantly, either. Until this survey was conducted, the amateur players had played basketball for 7.0 years, while the professionals had been playing for a statistically insignificantly longer period of 8.2 years. (Table 2).

Table 1. Structure of sample

Athletes	Number of players
Amateurs	60
Professionals	135
Total	195

Table 2. Average age and years of pracitcing basketball non-professionals and professionals

Athletes	Age	Year of practice
Amateurs	20.3	7.0
Professionals	21.3	8.2

RESULTS

A total of 2 265 injuries to the stomatognathic system were documented in this research; 200 (8.8%) of those injuries refer to the amateurs and 2 065 (91.2%) to the professionals. The most common injuries are lacerations and contusions to the oral soft tissues (a total of 2 208 or 97.5%), which amounts to an of average 11.32 lacerations per athlete per career, followed by dental injuries (a total of 57 or 2.5%) (Table 3). As far as lacerations to oral soft tissues are concerned, the most common injuries are lip lacerations 1 424 (64.5%), followed by 418 (18.9%)

Table 3. Injuries of the orofacial system

Athletes	Laceration	Dental injuries	Total
Amateurs	188	12	200
Professionals	2020	45	2065
Total	2208	57	2265

lacerations to the inner lining of the cheek, and 366 (16.6%) tongue lacerations (Table 4). The results of this research show that there is a difference between the total number of lacerations to oral soft tissues in the amateurs category, 8.5%, which is in average, 3.13 injuries per amateur per career (Table 5) and the professional category, 91.5%, which is an average of 14.96 laceration injuries per professional per career. Out of 135 professionals only 27.4% of them have not suffered a lip laceration during practice and 32.6% during a game. Only 44 athletes suffered an injury to the inner lining of the cheek during practice and 32 of them during a game, whereas 44 of them injured their tongue in practice and 35 of them in a game. It should be noted that among the interviewed professionals none of them had been injured on only one occasion, and only one amateur had been injured only once. During the course of his career one athlete had suffered as many as 80 lacerations to oral soft tissues (Table 6).

Out of all recorded laceration injuries 59.8% lacerations to oral soft tissues occurred during practice, while 40.2% of them occurred during games. Furthermore, during practice the amateurs suffered 12.6% of the lacerations to oral soft tissues, and the professionals 87.4%, while during games the amateurs suffered 2.5%, and the professionals 97.5% of lacerations.

A total of 57 dental injuries were recorded in this investigation, which were distributed as follows: 78.9% of the injuries occurred in professionals, and 21.1% in amateurs. More dental injuries occurred during practice 54.4% than during games 45.6%. A total of 44 of dental injuries were reported in this investigation, out of which 23 were tooth fractures occurring during practice, and 21 during games. One interviewee had a fracture of no less than four teeth on a single occasion, while 12 basketball players have each had one tooth fracture during the course of their career (Table 7). Out of 64 medically treated injuries to the stomatognathic system, as many as 48 (75%) of them were dental injuries treated by doctors of dental medicine, while 16 (25%) of them were treated by doctors of medicine (Table 8). Out of a total of 195 basketball players 93.3% of them had never tried to wear a mouthguard, while only 6.7% (13 players – 4 amateurs and 9 professionals) had at some

Table 4. Laceration of soft tissue

Athletes	Lip lacerations		Internal cheek lacerations		Tongue lacerations		Total	
	N	%	N	%	N	%	N	%
Amateurs	119	63.3	27	14.4	42	22.3	188	100.0
Professionals	1305	64.6	391	19.4	324	16.0	2020	100.0
Total	1424	100.0	418	100.0	366	100.0	2208	100.0

N - number of athletes

Table 5. Number of lacerations reported by amateurs on practice and games during career

Number of injuries		Laceration of soft tissues on amateurs athletes					
		Lips (p)	Lips (g)	Cheeks (p)	Cheeks (g)	Tongue (p)	Tongue (g)
0	N	39	51	51	60	48	59
	%	65.0	80.0	85.0	100.0	80.0	98.3
1	N	6	3	3		2	1
	%	10.0	5.0	5.0		3.3	1.7
2	N	3	3	3		4	
	%	5.0	5.0	5.0		6.7	
3	N	1		1		1	
	%	1.7		1.7		1.7	
4	N	3	3			2	
	%	5.0	5.0			3.3	
5	N	1		1		2	
	%	1.7		1.7		3.3	
6	N	2					
	%	3.3					
10	N	4		1		1	
	%	6.7		1.7		1.7	
14	N	1					
	%	1.7					

N - number of athletes; p – during practice; g – during games

Table 6. Number of lacerations reported by professionals on practice and games during career

Number of injuries		Laceration of soft tissues on professional athletes					
		Lips (p)	Lips (g)	Cheeks (p)	Cheeks (g)	Tongue (p)	Tongue (g)
0	N	37	44	91	103	90	100
	%	27.4	32.6	67.4	76.3	66.7	74.1
1	N	11	20	11	6	10	10
	%	8.1	14.8	8.1	4.4	7.4	7.4
2	N	18	11	8	6	13	11
	%	3.3	8.1	5.9	4.4	9.6	8.1
3	N	13	17	8	5	7	4
	%	9.6	12.6	5.9	3.7	5.2	3.0
4	N	1	5	3	2	2	3
	%	0.7	3.7	2.2	1.5	1.5	2.2
5	N	17	15	2	3	7	2
	%	12.6	11.1	1.5	2.2	5.2	1.5
6	N	4	4	1	3	2	1
	%	3.0	3.0	0.7	2.2	1.5	0.7
7	N	3	1				
	%	2.2	0.7				
8	N	3		1			
	%	2.2		0.7			
9	N	1	1				
	%	0.7	0.7				
10	N	13	8	6	5	1	1
	%	9.6	5.9	4.4	3.7	0.7	0.7
12	N	1	1				
	%	0.7	0.7				
15	N	4	3	3	1	2	2
	%	3.0	2.2	2.2	0.7	1.5	1.5
20	N	5	3				
	%	3.7	2.2				
30	N	1		1	1	1	1
	%	0.7		0.7	0.7	0.7	0.7
35	N	1					
	%	0.7					
50	N	1	1				
	%	0.7	0.7				
80	N	1	1				
	%	0.7	0.7				

N - number of athletes; p – during practice; g – during games

Table 7. Dental injuries

Athletes	Broken teeth		Loosened teeth		Avulsed teeth		Total
	Practice	Game	Practice	Game	Practice	Game	
Amateurs	7	2	0	2	1	0	12
Professionals	16	19	6	2	1	1	45
Total	23	21	6	4	2	1	57

Table 8. Treatment of injuries

Athletes	Doctor of Dental Medicine	Doctor of Medicine	Total
Amateurs	11	2	13
Professionals	37	14	41
Total	48	16	64

Table 9. Mouthguard use

		Practice		Games	
		N	%	N	%
Try to wear a mouthguard	Yes	12	6.2	9	4.6
	No	183	93.8	186	95.4
	Total	195	100.0	195	100.0
Regularly use of mouthgurad	Yes	2	1.0	1	0.5
	No	193	99.0	194	99.5
	Total	195	100.0	195	100.0

N - number of athletes

point tried to wear a mouthguard (Table 9). In addition to that, out of a total number of players (195) no less than 99% do not use a mouthguard on a regular basis, and only 1% (2 players – one professional and one amateur) use a mouthguard regularly during practice and games. The players who did use a mouthguard mostly used a type II mouthguard– boil and bite mouthguard (10 players – 3 amateurs and 7 professionals), while the type III – custom-made mouthguard, was only seldom used (3 players: 1 amateur and 2 professionals).

DISCUSSION

A great number of lip lacerations can be easily explained by anatomical reasons. At the point of receiving a direct blow to the stomatognathic system the lips are the first to be affected; this is further aided by the shape of the lips (slightly protruding outwards), their structure (delicate and soft mucous membrane of the lips, friable tissue) and their positioning (leaning against the teeth), whereby the layout of teeth and the position of the incisal edge to the lips result in different kinds of lip lacerations. Wearing a fixed orthodontic appliance in general causes even more laceration injuries in athletes, unless they are wearing a mouthguard (Kvittem et al. 1998, Salam & Caldwell 2008). Internal cheek lacerations mostly result from a bite to the inner lining of the cheek during a blow to the lower jaw. Tongue lacerations are less frequent, although these occur on average 1.9 times throughout an athlete's career, which implies that the tongue is also subject to injuries as shown in Table 4. The most common mechanism of tongue injury is a tongue bite, which results in heavy bleeding, and pain.

The significantly larger number of injured professionals can be explained by a longer time practicing sports, a larger number of practices during a season/career as well as many more games played. The longer the period spent playing a sport, the greater the possibility of an injury. The significant difference in the number of lacerations to oral soft tissues between the amateurs and the professionals can also be explained by their attitude towards their sport. For professional athletes sport is a means of earning a living, which affects their approach to the game as well as their desire to prove themselves and achieve professional success (i.e. earn more money), all of which leads to more injuries.

The difference between the incidence of injury during practice and injury during games can be explained by a greater number of hours spent practising as opposed to the hours spent playing scheduled games. The incidence of injury is increased by the progressive increase of fatigue and the subsequent lack of concentration during practice. A more leisurely and less concentrated approach to tasks by some players during practice may also lead to injuries. Such a large number of injuries during practice is not normally expected, firstly because during practice the game is played against a "known" opponent, and secondly because there is no pronounced rivalry among the players or between the teams. A lesser incidence of injuries during amateur games shows that amateurs tend to pay more attention while playing, and exercise a greater avoidance of the opponent and the injuries themselves. The likelihood of repetition of an injury is greater in athletes who have been injured at least once over the course of their career, regardless of whether this happened during practice or at a game. Although laceration injuries are relatively minor injuries, the total number of 2208 injuries is significant and calls for mandatory mouth protection for basketball players. Wearing an intraoral custom-made mouthguard would eliminate almost all internal cheek and tongue injuries, as well as lessen the number of lip lacerations.

The distribution of dental injuries such that professional players suffer more injuries can again be explained by a longer time playing the sport and by more practice hours during a season as well as by the fact that professional players play more scheduled games. The reason for a higher incidence of dental injuries during practice sessions is the greater amount of time spent in practice than playing scheduled games, where the usual ratio is 6:1 in favour of the practice. A lack of concentration during practice leads to more dental injuries, while at games players need to be more concentrated in order to achieve the best result possible. What is disconcerting is the number of broken teeth in basketball players. Tooth fracture is considered to be a major injury. Most of the dental injuries could have been mitigated with mouthguard use, and most of them would have probably even been prevented, since a mouthguard absorbs the energy of the blow and therefore reduces the possibility of hard and soft tissue damage by creating a mitigating effect on the direct blow to the teeth and dispersing the force which would have led to tooth fracture or luxation.

According to the literature, more than half of the injuries to the stomatognatic system occurring during sports activities refer to lacerations to oral soft tissues, mostly lip lacerations. Dental injuries are statistically in second place, while all other injuries are relatively poorly represented (Škrinjarić 1995). Diab and Mourino (Diab & Mourino 1997), Flanders and Bath (Flanders & Bath 1995) and Maestrello-de Moya and Primosch (Maestrello-de Moya & Primosch 1989) have noted almost identical results to those collected this investigation. Major injuries, or 22% of all injuries recorded in this investigation required medical attention. In research by Jerolimov et al. (Jerolimov et al. 2001) a total of 124 injuries to the stomatognathic system were recorded in a selected sample of basketball players, where 69.3% of these injuries refer to lacerations to oral soft tissues, while other injuries account for the remaining 30.7%. The difference in the percentage of lacerations to oral soft tissues is the result of a larger number of injuries studied by Jerolimov and associates and a smaller sample size. While dental injuries comprise 20.16% of all injuries in the research of Jerolimov et al., in our research dental injuries account for 2.5% of all injuries observed. Jerolimov et al. used a selected sample (professional basketball players – National Basketball Team), while our research encompasses a wider population of people participating in basketball (amateurs and professional basketball players). In other research, Dilberović et al. (Dilberović et al. 2004) recorded 160 injuries to the stomatognathic system in a sample of 53 basketball players. In this case lacerations to oral soft tissues accounted for 97.5%, and dental injuries for 2.5% of all injuries, which is a result similar to the one in this research.

Diab and Mourino (Diab & Mourino 1997) recorded similar results regarding the treatment of injuries observed in their research. Such a large number of medically treated dental injuries indicate their severity. Jerolimov et al. (Jerolimov et al. 2001) recorded that medical assistance was given in 35 cases. Medical treatment was provided in all cases of loosened or avulsed teeth, all injuries to or pain in the temporomandibular joint and all jaw fractures. Medical treatment was provided for 50% of all broken teeth, 55% of the lacerations to oral soft tissues and only in 25% of concussions. This research recorded more medically treated injuries to the stomatognathic system in professional athletes (79.7%) than in amateur athletes (20.3%). This is the result of a larger number of laceration and dental injuries suffered by professionals, the severity of these injuries that required medical assistance and the access to medical care. Out of 44 fractured teeth 56.8% of them were type III fractures – tooth crown fracture (enamel and dentine involvement) with a pulp opening. Such injuries require root canal treatment which constitutes a complicated dental injury. As many as 16 crowns were made as a result of these tooth fractures, and 7 bridges were fabricated in cases of avulsed teeth or subsequent tooth extractions due to serious fractures caused by heavy blows to the stomatognathic system. In the case of one basketball player alone a series of 4 teeth required root canal fillings.

Levin et al. (Levin et al. 2003) agree with the results of this research and state that, in Israel, 98.1% of basketball players do not use mouthguards, although 30.2% of them are aware of the advantages of using a mouthguards. Only 1.9% wear a mouthguard while playing basketball. Ferrari and Ferreria de Mederios (Ferrari & Ferreria de Mederios 2002) obtained similar results; they noted that 97.9% of basketball players do not use mouthguards, although 57.3% of them are aware of the advantages of using one. Only 2.1% of players wear a mouthguard during practice and at games. The results obtained by Maestrello-deMoya and Primosch (Maestrello-de Moya & Primosch 1989) show that 43 (4.2%) basketball players wore a mouthguard during the 1986/87 season, so it follows that in their research only 2 (4.7%) of the recorded lacerations to oral soft tissues did not require medical treatment, while in the 977 basketball players who did not wear a mouthguard, as many as 313 (32%) injuries were recorded. This illustrates that there is a 6.8% greater incidence of injury when a mouthguard is not used. All of the basketball players who wore a mouthguard did so voluntarily. In comparison with this study, an additional 3.2% of athletes wore a mouthguard while practicing basketball, even though the small number of basketball players in Maestrello-de Moya and Primosch's (Maestrello-de Moya & Primosch 1989) research who did wear a mouthguard while practicing basketball presented fewer injuries to the stomatognathic system. The research conducted by Jerolimov et al. (Jerolimov at al. 2001) shows that out of a total of 18 basketball players 10 of them had attempted to wear a mouthguard, and 9 of them wore one regularly. The results of Jerolimov et al. research differ from the results of this research in the type of the athletes interviewd, and the sample size. Most of those surveyed in investigation of Jerolimov and associates played in clubs abroad, outside the Croatian league so they are better informed about mouthguards, which is evident from the greater number of players using mouthguards.

It is possible to prevent injuries to the stomatognathic system by using intraoral custom-made mouthguards. Garon et al. (Garon et al. 1986) agree with the results of this research and recommend mandatory use of protective mouthguards in all sports with a larger number of players and a greater percentage of oral injuries. Maestrello-de Moya and Primosch (Maestrello-de Moya & Primosch 1989) and Diab and Mourino (Diab & Mourino 1997) also recommend mandatory wear of mouthguards for basketball players. The results of this research are consistent with the results obtained by McNutt et al. (McNutt et al. 1989) which demonstrate a significant percentage of injuries to the stomatognathic system present in unorganized American football, baseball and basketball, while at the same time there is an almost negligible number of players using

mouthguards. Morrow et al. as well as Ma (Morrow et al. 1991, Ma 2008) believe that doctors of dental medicine ought to emphasize the necessity of use of protective mouthguards in all sports where there is a possibility of suffering injuries to the stomatognathic system, and where is a greater incidence of injuries to the stomatognathic system.

CONCLUSIONS

It has been demonstrated that there is a significant incidence of injuries to the stomatognathic system related to practicing basketball (a total of 2 265 injuries). More injuries to the stomatognathic system were recorded in professional athletes (91.2%) than in amateur athletes (8.8%). The most common injuries are lacerations and contusions of the lips, cheeks and tongue 97.5% (8.5% amateurs and 91,5% professionals), followed by dental injuries, which account for the remaining 2.5% (21,1% in amateurs and 78,9% in professional players). Out of a total of 195 players only 1% (2 players – one professional and one amateur), frequently wear a mouthguard during practice and games, while only 6.7% (13 players - 4 amateur and 9 professional players) of them have attempted to wear a mouthguard. If basketball players frequently used intraoral mouthguards, there would be no injuries to the stomatognathic system or these injuries would be mitigated. It is therefore necessary to encourage more education and provide more information and guidance on protective mouthguards for basketball players, and also for the coaches, parents and dental professionals in order to increase their use.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 498-508 *Original paper*

COMPARISON OF TWO DIFFERENT METHODS (PATIENT QUESTIONNAIRE AND MEDICATION POSSESSION RATIO - MPR) FOR MEASURING THE CHRONIC PATIENT'S BEHAVIOR

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SUMMARY

Background: *Medication adherence is the extent to which patients take medications as prescribed by their health care providers. There are a number of approaches to study medication-taking behavior. The aim was to compare two most common methods for measuring adherence: Patient Adherence Questionnaire and Medication Possession Ratio (MPR). They belong to the indirect methods.*

Methods: *In this article four adherence studies were analysed and the results were compared, two wherein the patient questionnaire was applied and other two with medication possession ratio applied.*

Results: *The obtained results reveal that more than half of respondents (58.9%) experienced constant nonadherence behavior according to the prescribed therapy. The main reason of nonadherence is oblivion, suggesting that it is necessary to pay more attention to this problem.*

Conclusions: *Nonadherence with therapy has negative consequences on the health of the individual, and an adverse impact on the community health and wealth. Patients should be informed of the importance of regularly taking prescribed therapy. The main problem of long-term therapy is significantly decreased of adherence to medication in a very short time. It is important to stress that almost all the interventions effective for improving patient adherence in long-term care are complex and should be repeated after a while.*

Key words: *adherence - medication prescribing – patient's adherence questionnaire - medication possession ratio - pharmacy claims data*

* * * * *

INTRODUCTION

Medication adherence is generally defined as the extent to which patients take medications as prescribed by their health care providers (Dobbels et al. 2005). Therapy is the act of taking drugs on schedule or taking medication as prescribed. There are a number of approaches to study patient's medication-taking behavior. The most precise methods are directly observed therapeutic outcome, biological methods: measuring the level of medicine or metabolite (blood or urine drug concentrations). Other methods are clinician reports, pill counts, rates of prescription refills, electronic medication monitors, patient diaries, patient self-report scales. Questionnaires have the benefits of being cheap, easy to administer, non-intrusive, and able to provide information on attitudes and beliefs about medication.

There are a number of reasons why patients do not adhere or comply with their medication regimen (Jakovljevic 2014b). The common factors that interfere with medication adherence are social/economic-related factors (age, race, economic status, medication cost), survivor-related factors (forgetfulness, treatment anxiety, misunderstood instructions, fear of becoming dependent on medication), medication-related factors (length of treatment, complexity of treatment, unwanted side effects) and the condition-related factors (level of disability, severity of the condition).

Nonadherence greatly increases the nation's health care bill. The emphasis must be on the interventions on different levels (physician, pharmacist, newspapers, television and so on) with the aim to decrease nonadherenceand improve the therapeutic outcomes. Paradoxically, as cost-driven nonadherence pushes total health care costs higher, these same insurance companies may find themselves less profitable over the long run as they face the high cost of complications caused by medication nonadherence (Hofmann 2013).

The aim is to compare two most common methods for measuring adherence: Patient Adherence Questionnaire and Medication Possession Ratio (MPR) which belong to the indirect methods. Analyses of prescription refills can provide crucial insights into patient willingness to comply. This can be a valuable adjunct to medication management of the individual patient (Roth & Caron 1978, Goldberg et al. 1998, Dezii 2001).

Table 1. Description of four adherence studies

Study	Pharmacy	No. of patients	Method for adherence measurement	Published
Study 1	City pharmacy Zagreb (Gradska ljekarna Zagreb)	635	Self-report questionnaire	Culig J, Leppée M, Boskovic J. Eric M. Determining the difference in medication adherence between the general patient population and patients receiving antihypertensive therapy: A case study. Arch Pharm Res 2011; 34:1143-52. doi 10.1007/s12272-011-0712-0
Study 2	Pharmacies in Varazdin County	56	Self-report questionnaire	Fuckar S. Adherence to medication according to long-term therapy. Thesis. School of Medicine, Josip Juraj Strossmayer University Osijek, 2011.
Study 3	Private pharmacy in Zagreb	150	MPR	Leppée M, Boskovic J, Culig J, Eric M. Pharmacy claims data as a tool to measure adherence. Curr Med Res Opin 2012; 28:1389-93. Posted online on June 22, 2012. doi 10.1185/03007995.2012.705781)
Study 4	Pharmacy Atlantic Zagreb	142	MPR	Mandic-Zovko N. Measuring of adherence to therapy by Medication Possession Ratio (MPR). Thesis. School of Pharmacy and Biochemistry, University of Zagreb, 2014.

METHODS

Four adherence studies are analyzed (Table 1). The study 1 and 2 was designed as a cross-sectional survey by use of a self-administered questionnaire and in the studies 3 and 4 pharmacy claims data were used. The study 1 (Culig et al. 2011, Culig & Leppée 2014) included 635 individuals collecting or buying drugs for the treatment of chronic diseases, with special reference to subjects taking antihypertensive agents (n=361). A total of 1500 questionnaires were distributed of whom 635 (42.3%) questionnaires can be utilized in the statistical analysis. The survey was conducted at Zagreb pharmacies and the 33-item questionnaire was filled out by study subjects with instructions and help provided by the pharmacist as questionnaire administrator. The questionnaire was anonymous and study subjects could ask the pharmacist about any possible vagueness.

According to medication adherence behavior, study subjects were divided into two groups of adherent and nonadherent, as declared by them. The subjects answering the respective question that they had never failed to take their medication on time were considered as adherent, and all others as nonadherent. The questionnaire listed 16 common reasons for nonadherence and study subjects had to answer questions on each of these reasons as the possible cause of his/her nonadherence. These answers were used to analyze the impact of each of these reasons for nonadherence.

The study 2 was conducted in pharmacies in Varazdin County (Fuckar 2011). The survey was conducted in three pharmacies in the wider area of the city of Varazdin and two pharmacies in the town of Varazdin. A total of 100 questionnaires were distributed of whom 56 (56%) questionnaires can be utilized in the statistical analysis. Patients have occasion to raise drug prescribed prescription for a chronic condition in public pharmacies, voluntarily and anonymously completed the questionnaire with the help and guidance pharmacist. Adherence Scale Čulig (Appendix) is attached to the end of the work. All the respondents in terms of persistence to therapy were divided into the adherent and non adherent. The survey indicated 16 very frequent reasons of nonadherence. Based on the responses we analyzed the impact of individual reasons of nonadherence.

In the other two studies (3 and 4) pharmacy claims data were used. In study 3 data of 150 patients were analysed in one Zagreb's public pharmacy to find out the rate of adherence to chronic disease medication (Leppée et al. 2012). Three consecutive dates of filling/ refilling medications for each of 150 patients were analyzed; first at the beginning of the analysis period, followed by the second and third date when the patient is refilled medication. A first pharmacy record dating from the 5th October 2010 and last from 29th September 2011, which implies that the our small study involved pharmacy data in a period of about one year. MPR is used as a measure of adherence to chronic disease medication. The MPR is often defined as the sum of the days' supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last refill. This calculation usually results in a ratio less than 1.0 if there are lapses in prescription refilling. Early refilling would lead to an MPR of more than 1.0; the MPR in such a case is often truncated at the maximum value of 1.0, indicating the potential for perfect adherence.

We used the premise that pharmacy claims data and refilling the prescribed medication can be used to determine MPR, and that MPR can be used as a marker of patient adherence to prescribed medication; however, whether the patient consumed it as directed is not certain.

While the analysis of this information does not reveal whether a pill is actually being ingested, it can be reasonably assumed that patients would not continue to

refill a prescription without the intention to adhere. The inclusion criteria were having at least one prescription for chronic disease (long-term medication) in the beginning of the analysis period and during the analysis period (second and third refill). Adherence was measured as a function of the gaps between refills to provide timely information on the dynamics of patient medication adherence. We believe that identification of gaps in medication supply is clinically important. Creating a mechanism whereby clinicians are informed of these refill gaps might help stimulate early intervention, or improve the quality of otherwise scheduled clinical encounters (Hansen et al. 2010). Following past MPR-related studies (Bramley et al. 2006, Fung et al. 2007, Andrade et al. 2006) we take a patient as adherent to therapy only when his/her MPR for each medication is at least ≥80% (Mabotuwana et al. 2008).

In the study 4, that was the administrative claims study, the data on adult patients with multiple chronic disease treated with more than one medication on their first contact with the medication were used (Mandic-Zovko 2014). Authors used pharmacy claims data for 142 patients in one Zagreb's public pharmacy to find out the rate of adherence to chronic disease medication. Patients in this pharmacy receive supplies for various numbers of days (usually for 30 days) depending of kind of medication. Our study involved pharmacy data in a period of about half a year. We used the premise that pharmacy claims data and refilling the prescribed medication can be used to determine Medication Possession Ratio (MPR), and that MPR can be used as a marker of patient adherence to prescribed medication; however, whether the patient consumed it as directed is unknown. Following past MPR-related studies, we take a patient as adherent to therapy only when his/her MPR for each medication is at least ≥80%. The inclusion criteria were having at least one prescription for chronic disease (long-term medication) in the beginning of the analysis period and during the analysis period.

At each patient's visit to the pharmacy, a pharmacist recorded the type and quantity of prescribed and dispensed medication (according to the Anatomical Therapeutic Chemical (ATC) Classification for each medication), diagnosis, a total of up to ten drugs per patient, and some demographic data (name, age, gender). MPR with variable (start to end of therapy) as a measure of adherence to therapy were calculated. MPR was calculated by summing days supply from the first to the last prescription (inclusive) divided by the time between the last prescription date plus days' supply and the first prescription date. Variable MPR was evaluated for all patients and the continuously eligible cohort. Acceptable adherence was defined as an MPR of ≥80%. MPR for each medication is calculated for each patient. If the patient had more than one medication, calculated is average MPR per patient (for all medications). This study was conducted under the supervision of the Department of Pharmacoepidemiology, Andrija Stampar Institute of Public Health, Zagreb, Croatia.

Statistic analysis

Descriptive statistics were used to summarize patient demographics, adherence characteristics, medication variables, and the occurrence of discontinuation. Because the purpose of using refill records is to improve intervention efficiency and identify high risk patients, we focused on minimizing the false positive rate. Student's t-test, a Mann-Whitney Rank Sum test, Chi-square test and multiple linear regressions were used. The Mann-Whitney Rank Sum test was used to examine differences in adherence among patient subgroups. A significance level of $P<0.05$ was used when appropriate for the evaluation of the results. The analysis had enough statistical power to detect the significant difference that would have been evident if the statistical power had been greater. A priori, we set 20% as a threshold for the false positive rate that would be acceptable for clinical application of this method. All analysis was performed with SigmaStat 3.0 for Windows (SPSS Science software products, Chicago, IL, US).

RESULTS

Study 1

In study 1 more than half (n=361; 56.9%) of 635 study subjects were on therapy for arterial hypertension and also for some other diseases. A total 1,357 diagnoses were reported by survey respondents (i.e., an average of 2.1 diagnoses per respondent). The most common diagnoses were diseases of the circulatory system (n=500, 36.8%) and the group of endocrine, nutritional and metabolic diseases (n=285; 21.0%). The number of subjects increased with age, with almost two thirds (64.7%) of subjects older than 55, which is consistent with the known drug utilization increase with age. This relation was even more pronounced in the group of subjects treated for arterial hypertension. In the total study population (n=635), nonadherent subjects prevailed over adherent subjects (n=370; 58.3% vs. n=265; 41.7%). The rate of medication adherence was lower in the group of subjects treated for arterial hypertension as compared with total study population, however, the difference was not statistically significant (p=0.501). The rate of adherent and nonadherent subjects is shown in Table 2. The level of adherence was found to slightly increase with age, so the subjects older than 65 showed a higher level of medication adherence as compared with other age groups. A similar pattern was observed in the group of subjects with arterial hypertension; however, the difference did not reach statistical significance. There was no statistically significant difference in age distribution between total study population and subjects treated for arterial hypertension reporting medication adherence (P=0.298) and medication nonadherence (p=0.273). The great majority of study subjects stated forgetfulness as the main reason for skipping drug dose (n=381; 60.0%),

Table 2. Comparison of the adherence in the Studies 1-4

Study	Adherent		Nonadherent		Total		p
	n	%	n	%	n	%	
Study 1	265	41.7	370	58.3	635	100.0	p>0.5
Study 2	23	41.1	33	58.9	56	100.0	p>0.5
Study 3	54	36.0	96	64.0	150	100.0	p>0.5
Study 4	132	93.0	10	7.0	142	100.0	p<0.05

Table 3. Reasons for medication nonadherence in Studies 1 and 2

Reason for skipping drug doses	Study 1		Study 2	
	n	%	n	%
I just forgot	381	60.0	20	35.7
I was not at home	288	45.4	4	7.1
I fell short of the drug (I had consumed all of it)	282	44.4		
I had problems with the timing of the medication	260	40.9	4	7.1
I take a number of drugs several times a day	251	39.5	8	14.3
The drug was not available due to shortage of supply	228	35.9		
I was feeling well	228	35.9	8	14.3
I wanted to avoid side effects	188	29.6		
My doctor has frequently changed my therapy	165	26.0		
I felt the drug could be toxic/harmful	150	23.6		
I was feeling sleepy at the time of taking the medication	145	22.8		
I felt depressed or broken hearted	145	22.8		
I was afraid of developing drug dependency	143	22.5		
I had cold	133	20.9		
The drug was too expensive	132	20.8		
I did not want other people to see me while taking the drug	79	12.4		
Other			12	21.4

followed by not being at home (n=288; 45.4%) and being short of the drug (having used it all) (n=282; 44.4%) (Table 3). Like total study population, the majority of subjects treated for arterial hypertension reported forgetfulness as the main reason for medication nonadherence (n=220; 60.9%). The second most common reason was a drug shortage (n=169; 46.8%) and being away from home (n=163; 45.2%). Comparison of reasons for medication nonadherence in the total study population versus subjects on antihypertensive therapy showed no statistically significant difference in any of the reasons (P=0.895), indicating that subjects treated for arterial hypertension did not differ from the total study population according to the reasons for medication nonadherence. Analysis of reasons for medication nonadherence according to age groups in the total study population pointed to forgetfulness as the leading reason (61.0%) in the oldest and largest age group (66+; n=249) as well as in all other age groups. In the 66+ age group, the second leading reason for medication nonadherence was a drug shortage (41.4%), followed by taking a number of drugs several times a day (41.0%). The latter reason was not among the first three reasons in any other age group. Absence from home was the second leading reason in most age groups; however, in the 66+ age group it ranked only fifth reason for medication nonadherence. In the 56-65 age group, away from home and drug shortage were the second and third leading reasons for medication nonadherence (51.2% both).

There was no statistically significant difference among particular age groups according to the four leading and major reasons for medication nonadherence, indicating that age had no effect on these reasons. Analysis of reasons for medication nonadherence according to age groups in the group of subjects treated for arterial hypertension indicated forgetfulness as the leading reason (60.8%) in the oldest and largest age group (66+; n=166) as well as in all other age groups. In the 66+ age group, the second leading reason for medication nonadherence was taking a number of drugs several times a day (42.2%), and it ranked so high only in this age group. It was followed by a drug shortage (42.2%) and having problems with medication timing (37.3%). Absence from home ranked second in other age groups, while sharing only the sixth to seventh place in the 66+ age group. In the 56-65 age groups, absence from home ranked second (52.9%) and shortage of drug third (51.0%), the same pattern being recorded in the 46-55 age groups. There was no statistically significant difference among particular age groups according to the four leading reasons for medication nonadherence (P=0.171), suggesting that age had no impact on the reasons for medication nonadherence in subjects treated for arterial hypertension either. In the latter, age had no effect on the reasons for nonadherence, i.e. the same

pattern was recorded across all age groups, although forgetfulness was expected to be more common in older age groups.

Study 2

In the study 2, there were 56 patients of all ages included. Most of the respondents were in the middle age groups, i.e. 40-69 years of age (n=44, 78.6%). In particular, in the range of 40-49 years in the survey were attended by 15 participants, or 26.8% of all respondents. At the age of 50-59 years participated in 16 respondents, or 28.6 % of all respondents, as this age group makes the most members. Also a large number of respondents (n=13) were in the age group of 60-69 years in the percentage of 23.2% of all respondents. Of the total number of subjects (n=56), there were more nonadherent (n=33, 58.9%) than adherent (n=23, 41.1%).

Considering the relatively small number of subjects in the study (n=56), only the respondents in the middle age groups (40-69 years) were analyzed and it was found again that adherence increases with age. In the age group 40-49 were 33.3% adherent subjects, in the next age group (50-59 years) adherent subjects increased to 43.8%, and in the next age group (60-69 years) participation of adherent subjects were 46.2%. Women were significantly more adherent than men (60.9%:39.1%). Of the listed reasons, the most of the respondents indicated oblivion (n=20, 35.7%) as the main reason of nonadherence. As the second and third reason follows the taking multiple medications several times a day and good sense (n=8, 14.3%). On the fourth and fifth place were the fact that he/she was not at home and that he/she had problems with taking the drug at a specific time (n=4, 7.1%).

Respondents were the most frequently treated from diseases of the heart and blood vessels (n=44, 45.4%), accounting for almost half of all diagnoses (n=97).

Study 3

The study 3 was a pilot study which includes 150 patients with chronic disease medications prescribed. According Medication Possession Ratio (MPR) the most patient were nonadherent (n=96; 64.0%). Most patients (n=130, 86.7%) were with one or more ATC group C (cardiovascular) medication prescribed. There was not a significant difference between adherence for all patients with prescribed chronic disease medication, patients with prescribed ATC group C medication and patients with medication other than group C (p=0.333).

It needs to be noted that herein we present an analysis using overall MPR and C medication MPR, but the same analysis can be carried out on a drug class specific basis as well (using the drug class specific MPRs) if required. Medication nonadherence due to cost issues among study patients was evaluated. We analyzed patients with and without co-payment for medication. Adherence was surprisingly slightly higher in those without co-payment, but there is no difference among these two groups of patients (p=1.000).

We analyzed up to five medications per patient. The most patients used a combination of two (n=44, 29.3%) and three (n=34; 22.7%) medications. There was no difference between patients with different number of medications (from one to five) according to adherence rate (p=0.071).

Study 4

In study 4 were included 142 patients with chronic disease medications prescribed. The female patients predominated over the male (female: n=75; 53.5%, male. n=67; 46.5%). The patients were mostly older than 70 (n=57; 40.1%) and in the 60-69 age group (n=48, 33.8%). Almost two-thirds of patients were 60+ (n=105; 73.9%). We analyzed up to a maximum ten medications per patient. The most patients (n=92; 64.8%) used two (n=54; 38.0%) and three (n=38; 26.8%) medications. Only 28 patients (19.7%) take only one drug (single medication). All study patients have taken 485 medications, what is the average of 3,42 per patient. Initial MPR in the initial phase was in 132 patients (93.0%), 80%≤MPR, which means that they were adherent to medication. Over time, that rate has decreased (only 15.0% at fifth refill!).

For the duration of drug taking, adherence to therapy continuously was falling and the number of patients with the same MPR was reduced. After three refills 100% ≤MPR patients are reduced for one-third (35.3%). A number of the patients with initial MPR 90% ≤MPR<100% reduced for three-fourth (73.8%) and the patients with 80% ≤MPR<90% halved (for 54.5%) (Table 4).

Table 4. Comparison of Medication Possession Ratio (MPR) among Study 3 and Study 4

	Study 3		Study 4	
MPR Condition	n	%	n	%
100% ≤MPR			68	47.9
90% ≤MPR<100%	54	36.0	42	29.6
80% ≤MPR<90%			22	15.5
60% ≤MPR<80%	78	52.0	7	4.9
40% ≤MPR<60%	15	10.0	2	1.4
MPR<40%	3	2.0	1	0.7
Total	150	100.0	142	100.0

There was some different number of refills among study patients. The most patients had four refills (57; 40.1%), followed by three refills (33; 23.2%). Long-term drug therapy decreased the adherence. As people take a medication a longer time, adherence to this medication more decreases. Difference among first and last MPR is bigger at the high number of refills. This means increasing the drop of adherence to medication according to the number of refills. During the five refills adherence to therapy decreased by 51.2% (from 100.%

to 48.8%) and after only two refills it decreased by 17.7% (from 100.0% to 82.3%). The difference in the median values between all two groups (first and last) in any refill number was a statistically significant ($p \leq 0.001$). There was no statistical significant difference between numbers of medications, according to adherence to therapy. There is no statistic significant difference among medications for different diagnosis, according to MPR Average MPR is a 103.4 indicating excellent adherence to medication regardless of type of disease. In the initial phase of testing they probably had a stock of medications and towards the end of the study MPR decreased, so that the average MPR is high.

DISCUSSION

In present article we compared two most common methods for measuring adherence: Patient Adherence Questionnaire and Medication Possession Ratio (MPR) which belong to the group of indirect methods. The common characteristic of both methods is the degree of adherence, but in all other aspects, patient questionnaire has the advantages: someone can get many other data related to patient, such as demographic, social, economic and other characteristics, the relationship between patient, physician and pharmacist, data about patients' diseases and many other data. MPR is simple in regard to the questionnaire, but is cheaper and easier to perform because it uses pharmacy claims data and do not require the work of interviewers. Among the many reasons people give for not adhering to drug treatment, forgetfulness is the most common. The key question is: Why do people forget? Sometimes, the psychological mechanism of denial is at work. Having a disorder causes concern, and having to take a drug as a constant reminder. Or, something about the treatment, such as possible side effects, may greatly concern the person, resulting in a reluctance to follow the plan. By discussing concerns, people can learn that denial of their disorder and misconceptions about their treatment can lead to forgetting to take drugs as prescribed, resulting in unwanted effects and therapeutic failure (The Merck's Manuals 2007).

Research on adherence has typically focused on the barriers patients face in taking their medications. Common barriers to adherence are under the patient's control, the interventions toward them are necessary step in improving adherence behavior. The typical reasons cited by patients for not taking their medications included forgetfulness (30 percent) (Osterberg & Blaschke 2005). The absence from home could also be associated with forgetfulness since the patient should have thought about dosing scheme and bring drug along when going out. The next reason reported by study subjects was shortage of drug, which could also be related to forgetfulness, i.e. failure of drug supply on time. Positive attitude towards own ability to comply with physician's medication instructions predominated over negative attitude in all age groups. A similar pattern was also recorded in the group of subjects treated for arterial hypertension, although higher motivation for regular therapy administration was expected in older hypertensives. Hypertensive subjects showed a statistically significantly higher rate of positive attitude towards treatment and ability to comply with medication instructions than those that were not sure about it. Self-reported medication taking adherence behavior of 132 high blood pressure patients was analyzed using an expanded version of the health belief model. Bivariate analysis showed that control over health matters, depend on providers, perceived barriers, duration of treatment, and others' nonconforming experience were significantly related to adherence ($p<0.05$). Log-linear multivariate analysis revealed that three of these five variables-control over health matters, perceived barriers, and duration of treatment-contributed independently to patient adherence. Self-reported medication taking was significantly related to blood pressure control ($p<0.02$). These data provide the basis for developing interventions for providers to facilitate the medication taking behavior of clinic patients (Hershey et al. 1980).

Patients with chronic diseases such as asthma, hypertension and diabetes have difficulty in adherence to prescribed therapy, resulting in unsatisfactory control of the disease.

Problem of adherence can be seen in all the situations when it is necessary that the patient is receiving therapy alone, regardless of the type and severity of the disease and the availability of health care. Low persistence is the main reason for lack of clinical benefit of therapy. It causes medical and psychosocial complications of the disease, reduces the quality of patients' lives, and wasted health resources. It is necessary to maintain a high adherence, because the patients with high levels of adherence have a significantly lower risk of cardiovascular disease. Patients who are within 120 days after the myocardial infarction took a single dose of the prescribed therapy had an increased likelihood of death by 80 % compared to those who took, and those who have taken some medication had a 44 % greater chance of death (Jackevicius et al. 2008). Often, patients discontinue therapy within one year of the first prescription (Kulkarni et al. 2006). The patients who are treated with antihypertensive but lowering therapies perseverance is poor, a third of them are persistent within 6 months (Chapman et al. 2005). Only 26 % of elderly patients who started taking statins to reduce the risk of coronary heart disease are retained high level five years later. The largest decline occurred perseverance during the first 6 months (Benner et al. 2002). We have found that in patients with age slightly increases the degree of persistence and the elderly show a higher degree of persistence than other age groups, corresponding to the data found in the literature (Morris et al. 2006). In

developed countries, people over the age of 60 spend about 50% of all prescribed drugs (about three times more per capita than in the general population) and are responsible for 60 % of all costs related to drugs, even though they're only 12% to 18% of the population in these countries (Eney & Goldstein 1976).

In that study nonadherent subjects prevailed over adherent (64.0%) which was slightly higher rate than in our Croatian studies (adherence has been based on patient self-report (58.3%). The similar difference is found in nonadherence to cardiovascular and antihypertensive therapy in both studies (63.1%/60.7%). We used pharmacy claims data for a small group of chronic patients and sought to identify a medication gap length between refills that may be useful in introduction action to improve patient adherence. The lengths of gaps varied in great range from eight months to lower. Some authors found that gaps between 8 and 19 days were highly predictive of discontinuation without exceeding a 20% false positive rate. Through electronic prescribing records, general practices can identify substantial levels of long-term medication adherence problems (Mabotuwana et al. 2009). There is some vagueness about measurement of adherence to therapy by prescription claims data. Many people obtain drugs regardless of the needs and refill or pharmacy claims data cannot be a true indicator of timely taking medications. After five refills (months), only 48.6% of patients are adherent to therapy. Clinicians tend to overestimate medication adherence, inadequately detect poor adherence, and may therefore miss important opportunities to intervene to improve antiretroviral adherence (Miller et al. 2002). For example, one study addressing differences in adherence between a one-pill combination-drug therapy and a two-pill polytherapy shows an adherence benefit with combination products (Dezii 2000). Many interventions to improve patient adherence are unsuccessful and sound theoretical foundations are lacking.

Comparisons are difficult, due to differences in adherence measures, intervention methods and in study populations (Dodds & Rebair-Brown 2000). The problem of prescription claims data is inability to verify regularity of medication intake, although the patient regularly purchases a medication. For patients in the most countries it is common to fill 90-days supplies of maintenance medication using retail or mail order channels. In Croatia patients refill medications as needed and only by retail. We used pharmacy claims data for a small group of chronic patients and sought to identify a medication gap length between refills that may be useful in introduction action to improve patient adherence. The lengths of gaps varied in a great range among patients and the same patient raises a variety of drugs in different terms.

Poor adherence to medications is associated with worse health outcomes (Ho et al. 2006, Simpson et al. 2006) and increased health care costs (McCombs et al. 1994). Furthermore, many factors associated with poor adherence have been identified, including but not limited to increase cost-sharing, pill burden and regimen complexity, side-effects, and patient beliefs about whether the drugs actually improve their health. Again, it is noteworthy that these studies almost universally measure the effect of interruptions (secondary nonadherence) or discontinuations (lack of persistence) with chronic medical therapies that have actually been started. Improving adherence to exercise, diet, and medication as well as focusing on addictive disorders such as smoking cessation requires patient, provider, and health care system combined approach (Miller 2011). The placebo and nocebo phenomenon and its psychobiological underpinnings, as well as mastering placebo-nocebo responses in everyday clinical practice must be taken into account (Jakovljevic 2014a). It can change a patient's sense of health and significantly affect the patient's adherence to medication. Further research of this effect is needed.

Person-centered medicine method for improving adherence can be remembered by the acronym SIMPLE: Select medications respecting the patient's preference and Simplify the regimen; Increase knowledge; Modify negative patient's attitudes and behaviors; Provide person-centered pharmacotherapy and motivational interviewing; Leave paternalism and empower patients to self-manage their medical condition; and Evaluate adherence regularly (Jakovljevic 2014b).

Limitations

The limitations of this report include several factors as: the consideration of a relatively small sample of patients, claims data within single pharmacy in Zagreb, the results may not be generalizable, in case of medication switching adherence is difficult to measure with pharmacy claims data and some patients may have additional drug use not captured within the claims database (e.g., samples, cash purchases). MPR does not provide accurate information on the continuity of medication usage and the precise measurement of each medication adherence, identification eventually drug stockpiles, measurement of gaps in medication supply with special emphasis on the allowable gap to obtain a refill of medications and calculation of a grace period are some attempts to remedy this limitation. The combination of an MPR and an adherence metric could provide timely information on the dynamics of patient medication adherence. MPRs rely on the accuracy of the days' supply figure provided by the pharmacist. In the case of inhalers, injectables and liquids, these figures are notoriously unreliable, so the reporting of an MPR is simply not appropriate for many medications. For oral pills, the problem is less significant but comes into play when different drug dosages have price parity and/or pill-splitting is common (Motheral. 2013). Study limitations included also lack information on reasons for medication initiation and discontinuation, severity of disease symptoms, and use of over-the-counter medications.

CONCLUSIONS

The both methods used reveal that more than half of respondents (cca 58%) experienced constant nonadherence according to the prescribed therapy. However, a difference between these methods in terms of determining the rate of adherence is not statistically significant. Nonadherence with therapy has negative consequences on the health of the individual, and an adverse impact on the community. The main reason of adherence is oblivion, suggesting that it is necessary to pay more attention to this problem. Patients should be informed of the importance of regularly taking prescribed therapy, and in agreement with them to figure out a good way to remind them to take the prescribed therapy. Of great help could be various applications for alerting on mobile devices that are now in mass use. After analyzing the reasons of nonadherence, we conclude that the adherence to the medication increases with age.

The main problem of long-term therapy is significantly decreased of adherence to medication in a very short time after prescribing. It is important to remember that almost all the interventions effective for improving patient adherence in long-term care were complex, including a combination of more convenient care, information, reminders, self-monitoring, manual telephone follow-up, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, and supportive care (Haynes et al. 2008).

Acknowledgements: None.

Conflict of interest : None to declare.

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Appendix. Adherence Scale Culig

A. General information

1. Age
   a) 26-35
   b) 36-45
   c) 46-55
   d) 55-65
   e) 65+
2. Gender
   a) male
   b) female
3. Employment
   a) employed
   b) unemployed
   c) retired
   d) beneficiary of social assistance
   e) student
   f) housewife
   g) farmer
   h) other
4. Education
   a) university degree
   b) bachelor degree
   c) high school
   d) primary school
   e) non of stated
5. Croatian veteran
   a) yes
   b) no
6. Do you live alone
   a) yes
   b) no
7. Marital status
   a) married
   b) divorced
   c) widower/widow
   d) extra-marital relationship
   e) never married
8. Disability
   a) yes
      if yes, what percentage?_____
   b) no

B. These questions revealed the subject's attitude towards his ability to comply with the physician's instructions and whether he/she believe his/her therapy to be beneficial for his/her health

	Question	I am not sure at all	I am quite sure	I am very sure	I am absolutely sure
1.	Are you sure you will be able to comply with your physician's medication instructions?	0	1	2	3
2.	Are you sure that treatment will be positive for your health?	0	1	2	3

C. Community (family and friend) support in your health treatment

	Question	I am very unsatisfied	I am mostly unsatisfied	I am mostly satisfied	I am very satisfied
1.	Are you satisfied with the support of your family and friends?	0	1	2	3
2.	Do your family and friends remind you to take medication on time?	0	1	2	3

D. When was the last time when you failed to take your medication

1. last week	□	4. 1-3 month ago	□
2. 1-2 week ago	□	5. more than 3 months ago	□
3. 3-4 week ago	□	6. I never fail to take my medication on time	□

E. People do not take their medication for various reasons. Here is a list of reasons for not taking your medication/drug

	Cause of nonadherence	Never	Very rare (1-2 yearly)	Sometimes (3-5 yearly)	Often (more than 5 yearly)
1.	I was not at home	0	1	2	3
2.	The drug was not available due to the short supply	0	1	2	3
3.	I just forgot	0	1	2	3
4.	I take a number of drugs several times a day	0	1	2	3
5.	I wanted to avoid side effects	0	1	2	3
6.	I did not want other people to see me taking drug	0	1	2	3
7.	My doctor frequently changes my therapy	0	1	2	3
8.	I felt the drug to be toxic/harmful	0	1	2	3
9.	I felt sleepy at medication time	0	1	2	3
10.	I had cold	0	1	2	3
11.	I felt depressed or broken	0	1	2	3
12.	I had problems with taking medicine at specific time (eg. with meal, on an ampty stomach)	0	1	2	3
13.	I have ran out of medication	0	1	2	3
14.	I felt well	0	1	2	3
15.	I was afraid of developing drug dependence	0	1	2	3
16.	The drug was too expensive	0	1	2	3

F. How often during the last week you

	Question	Never	Rarely	Sometimes	Often
1.	Felt sad	0	1	2	3
2.	Felt lonely	0	1	2	3
3.	Were down in the mouth	0	1	2	3
4.	Had difficulty with memory	0	1	2	3

G. How often during the last month you

	Question	Never	Rarely	Sometimes	Often
1.	Were upset because something unexpected happened	0	1	2	3
2.	You were confident that you can solve your problem	0	1	2	3
3.	You were nervous or stressed	0	1	2	3
4.	You had a feeling that problems accumulated and you can not solve them	0	1	2	3

H. Health habits

1. How often do you exercise actively (cycling, brisk walking, jogging, etc.)?
   - Never
   - Less than once a week
   - 1-2 times a week
   - 3-4 times a week
   - 5 or more times a week

2. How often do you drink alcohol?
   - Every day
   - Almost every day
   - 3-4 times a week
   - 1-2 times a week
   - 2-3 times a month
   - Once a month
   - Never

I. Did you have health problems during the month?

	Health problem	I did not have this health problem	I had this health problem			
			It does not matter	Bothers me a little	Bothers me a quite	Bothers me very much
1.	Fatigue	0	1	2	3	4
2.	Fever or cold	0	1	2	3	4
3.	Vertigo	0	1	2	3	4
4.	Pain or stiffness	0	1	2	3	4
5.	Problem with memory	0	1	2	3	4
6.	Nausea or vomiting	0	1	2	3	4
7.	Diarrhea	0	1	2	3	4
8.	Depression	0	1	2	3	4
9.	Nervousness, anxiety	0	1	2	3	4
10.	Insomnia sleepiness	0	1	2	3	4
11.	Skin changes	0	1	2	3	4
12.	Cough	0	1	2	3	4
13.	Headache	0	1	2	3	4
14.	Loss of appetite	0	1	2	3	4
15.	Abdominal bloating	0	1	2	3	4
16.	Pain in muscles and joints	0	1	2	3	4
17.	Sexual problems	0	1	2	3	4
18.	Weight changes	0	1	2	3	4

J. - 1. Claims about relationship with your family physician

	Relationship with family practice	Yes	No
1.	I can contact my doctor whenever I have personal or emotional problem	0	1
2.	I go to the doctor for preventive examinations	0	1
3.	My doctor knows if I live healthy (nutrition, smoking, alcochol)	0	1
4.	Sometimes my doctor does not listen me	0	1
5.	I do not always feel comfortable asking my doctor questions	0	1
6.	My doctor monitors my problem solving (either directly or by telephone)	0	1
7.	My doctor knows how much my family affects my health	0	1
8.	The doctor always explains me the results of laboratory tests, X-rays and other specialist findings	0	1
9.	I notice that my doctor advises and collaborates well with other healthcare professionals (eg pharmacists, nurses, etc.)	0	1

J. - 2. Pharmacist's questions and advice offered to the patient

	Questions and advices	Always	Sometime	Never
1.	Has the pharmacist asked you whether you took the drug for the first time	0	1	2
2.	Has the pharmacist asked you to repeat aloud the instructions on how to take the drug	0	1	2
3.	Has the pharmacist informed you on the importance of complying to the therapy prescribed	0	1	2
4.	Has the pharmacist advised you in detail on how to take the drug	0	1	2
5.	Has the pharmacist advised you on combining your therapy with OTC drugs	0	1	2
6.	Has the pharmacist advised you on solving the possible drug side effects	0	1	2
7.	Has the pharmacist asked you about skipping your therapy doses and why	0	1	2
8.	Has the pharmacist asked you about your attitude towards your drug therapy	0	1	2

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 509-512 *Original paper*

THIRTY YEARS OF USING A SERIES OF PERSONALITY QUESTIONNAIRES CONSTRUCTED BY COMPUTER

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SUMMARY

Background: *The series of personality questionnaires constructed using a computer was created on the basis of cybernetic theories of personality, which presupposes the existence of six conative control systems: a system for the regulation of defense responses, a system for the regulation of attack responses, a system for controlling physiological functions, a system for coordination of regulatory functions, system for integration of regulatory functions and system for regulation of activity. Six personality questionnaires measure the intensity of the following pathological personality tendencies: 1. neurasthenia and anxiety, 2. aggressiveness and impulsiveness, 3. conversive neurotic disorders, 4. psychotic dissociation, 5. psychotic regression and 6. extroversion-introversion.*

Subjects and methods: *The sample consisted of 4368 persons: 3496 subjects without a diagnosis, and 872 patients with a psychiatric diagnosis. Participants had to fill in the six personality questionnaire. Data were collected anonymously, during psychological treatment at the Neuropsychiatric Hospital "Dr. Ivan Barbot" in Popovača, at the Department of Occupational Medicine and Transport and the Department of Mental Health and Addiction Prevention at Dr. Andrija Štampar Institute of Public Health and for the purpose of selection of candidates for employment in the period from 1984 until today. Basic metric characteristics were determined for all scales. Factor structure of the scales was determined using principal component analysis; as canonical discriminant analysis, polar taxons analysis and canonical correlation analysis are special cases of factor analysis, results of factor analysis were used for further processing.*

Results: *Results from earlier studies are replicated on much larger sample: metric characteristics of scales are very good, as in previous studies, similar structure of polar taxons was found and discrimination between healthy subjects ad those with psychiatric diagnoses was successful. Canonical correlation analysis showed interconnection of reactions on certain scales and extremely complex relationship between them which indirectly confirms the theoretical model on the basis of which the scales are formed.*

Conclusions: *The usefulness of this scales is confirmed in clinical setting and in selection of candidates for employment.*

Key words: *cybernetic personality theory - personality questionnaires- multivariate analysis*

* * * * *

INTRODUCTION

Cybernetic theory of personality, emerged in the Faculty of Kinesiology (Momirović et al. 1982, Momirović & Ignjatović 1977), assumes the existence of a finite number of conative control systems, which are responsible for human adaptation to the environment. The adjustment is done by changing behavior, which responds to specific external conditions.

Conative control systems are specialized, each of which responds to certain environmental conditions and produces a certain type of reaction, which is evident in the behavior of people. Conative regulatory systems are hierarchically organized; some of them are superior to others, whereby the control range is greater for higher-level control system. Conative regulatory systems are interconnected by unidirectional, bidirectional and complex relationships. The intensity of the reactions of each controller is different, from barely noticeable to very strong reactions. Conative regulatory systems and cognitive mechanisms are at a healthy personality structure slightly positively correlated, but the dysfunction of conative regulators provokes a negative and significant impact on cognitive mechanisms.

The cybernetic personality theory assumes that conative regulation systems almost completely describe the structure of personality and explain each mode of behavior. In doing so, there is no dichotomy between normal and pathologic characteristics; they differ only in intensity (if the intensity is too high, the reaction is unadjusted to the environment).

The cybernetic personality theory assumes that there are six conative control systems:

- A system for the regulation of defense responses (Alpha) reacts to situations of threat, controls escape or blocks movement; it is associated with feelings of fear and in the case of dysfunction asthenic occurs neurotic syndrome (anxiety, obsession, compulsivity, phobia, hypersensitivity).
- A system for controlling attack reactions (Sigma) reacts to the situation of distractions or obstacles, the reaction is physical or verbal assault; it is associated with a sense of anger and in the case of dysfunction occurs stenic neurotic syndrome (aggressiveness, impulsivity).
- A system for the regulation of organ functions (Chi) reacts to body violation possibility, reactions are protective, avoiding pain or fatigue; dysfunction causes the formation of somatization or conversive neurotic reaction.

- A system for coordinating regulatory functions (Delta) coordinates the work of conitive, cognitive and motor controller; it provides adequate response and it is superior to most other systems; in case of dysfunction occur psychotic manifestations – paranoia, schizophrenia, loss of connection with reality.
- A system for integration of regulatory functions (Eta) ensures the functioning of a person in a social environment, regulates behavior in accordance with social regulations, in the case of dysfunction, occur psychotic (if coordinating system dysfunction is present too) or psychopathic (if the system for controlling attack reaction is also dysfunctional) symptoms.
- A system for the activity regulation (Epsilon) regulates the sleep-wake state, concentration and activity level; in case of dysfunction occur abulic or depressive symptoms (if the system for coordinating regulatory functions is present to). Manic disorder appears in the case of hyperactivity.

The aim of the work is a replication of the already well-known studies (Prot & Momirović 1984, Momirović 1988, Momirović 1989) on the far larger sample.

SUBJECT AND METHODS

Subjects

The sample consisted of 4368 persons: 3496 subjects without a diagnosis, and 872 patients with a psychiatric diagnosis, of which 261 psychoses, 283 with unspecified disorder (category in obs.), 28 alcoholics, 26 borderline personality disorder, 23 epilepsy, 13 patients with so-called. nuclear neurosis, 104 neuroses, 26 drug addicts, 15 patients with organic personality disorder, 63 patients with posttraumatic stress disorder and 30 patients with antisocial personality disorder. Data were collected anonymously, names of subjects were not recorded, only diagnostic category.

Methods

A series of personality questionnaires constructed by computer was created on the basis of cybernetic theories of personality. It consists of six scales with 30 items:

- Alpha Scale, which measures the intensity of interference from the circle of neurotic asthenia;
- Sigma Scale, which measures the intensity of aggressive and impulsive reactions;
- Chi scale, which measures the intensity of conversive and psychosomatic neurotic reactions;
- Delta scale, which measures the intensity of psychotic dissociation;
- Eta Scale, which measures the intensity of regression;
- Epsilon scale, which measures th;
- e intensity of the general activity.

Data were collected during psychological treatment at the Neuropsychiatric Hospital "Dr. Ivan Barbot" in Popovača, at the Department of Occupational Medicine and Transport and the Department of Mental Health and Addiction Prevention at Dr. Andrija Štampar Institute of Public Health and for the purpose of selection of candidates for employment in the period from 1984 until today.

Statistical analyses

Basic metric characteristics were determined for all scales (Momirović 1983). The factor structure of the scales was determined using principal component analysis; as canonical discriminant analysis, polar taxons analysis and canonical correlation analysis are special cases of factor analysis, results of factor analysis were used for further processing.

RESULTS

Results from this study are extremely extensive. For that reason, here are listed partially. Complete results are available at Dr. Andrija Štampar Institute of Public Health in Zagreb.

From basic metric characteristics of the scales we will list their reliability expressed as Kuder-Richardson coefficients of internal consistency in table 1.

Table 1. Reliability coefficient (Kuder-Richardson)

Scale	Coefficient
Scale Alpha	0.938
Scale Sigma	0.929
Scale Chi	0.956
Scale Delta	0.965
Scale Eta	0.950
Scale Epsilon	0.943

As can be seen, scales are highly reliable. There are also high coefficients of homogeneity and discrimination of individual items.

Taxonomic analysis of polar taxons substantially replicated taxonomic dimensions from earlier study (Table 2).

Table 2. Polar taxons

I	general psychopathology
II	primary aggressiveness
III	neuroticism
IV	neurasthenia
V	hysterical regression
VI	regression

Table 3. Means of groups (standardized values)

Diagnosis		Alpha	Sigma	Chi	Delta	Eta	Epsilon
Without diagnosis	ND	0.26	0.17	0.30	0.31	0.27	-0.20
Alcoholism	AL	-0.94	-0.67	-1.04	-1.20	-0.74	0.95
Borderline Personality Disorder	BP	-1.77	-1.03	-2.14	-2.14	-1.87	1.43
Epilepsy	EP	-1.04	-0.88	-1.52	-1.46	-1.37	0.80
No specified, „In Obs.“	IO	-0.65	-0.54	-0.71	-0.70	-0.63	0.41
Neurosis nuclearis	NN	-2.16	-1.54	-2.42	-2.01	-2.26	1.38
Neurosis	NE	-0.94	-0.53	-1.10	-0.91	-0.78	0.58
Drug addiction	DA	-0.53	-0.81	-0.76	-0.78	-0.56	0.57
Organic disorder	OD	-0.85	-0.26	-0.53	-0.57	-0.30	0.63
Post-Traumatic Stress Disorder	PT	-1.11	-0.96	-1.45	-1.69	-1.37	1.47
Sociopaths	SC	-0.79	-1.31	-0.89	-1.15	-1.12	0.13
Psychosis	PS	-1.47	-0.70	-1.71	-1.75	-1.60	1.13

It is interesting to note that the fifth taxonomic dimension was identified as hysterical dissociation in earlier study, which often recalls the opinion of one of the authors (Momirović 1995) of cybernetic theory of personality on the absence of Eta factor (i.e. conative regulation system for integration of regulatory functions). Eta factor does not appear in all researches for the simple reason that many studies were conducted on a sample of soldiers and it is well known that each recruitment process in any army in the world is focused on the elimination of individuals who cast doubt on the military subordination, i.e. obedience to superiors. It is logical that in such samples, there are few people who fall under the diagnosis „antisocial personality disorder“, or as it is usually called: psychopathy (or sociopathy), and as required by the cybernetic theory of personality, dysfunction conative system for integration of regulatory functions (Eta) is one of the causes of the so-called sociopathic ways of responding (lack of empathy, disregard for authority, individualism, aggression).

Canonical discriminant analysis revealed significant differences among examined groups and the highest between subjects without any diagnosis and other groups. It is interesting to note that the nature of these differences is such that allows the use of these personality questionnaires as screening instruments: in practice, subjects with any diagnosis at first sight react very differently from those without psychiatric diagnosis and this is evident even in the simplest possible method of calculating the total score, i.e. in plain addition of numerical values associated with individual response (here are listed standardized, Z-values) (Table 3).

Four significant discriminative dimensions were found in canonical discriminant analysis, where the first one represents so-called general pathology dimension, second one is defined by aggressive reactions, third one differs patients diagnosed with so-called major personality disorders (psychosis, neurosis nuclearis, borderline personality disorder) from all others – this dimension is bipolar (neuroticism vs psychoticism) and fourth differs subjects with so-called sociopathic personality disorder from all others (Table 4, Table 5, Table 6).

Table 4. Structure of discriminant dimensions

	D 1	D 2	D 3	D 4
Alpha	0.796	-0.077	0.209	0.311
Sigma	0.490	0.637	0.266	0.470
Chi	0.933	0.008	0.119	0.320
Delta	0.945	0.202	-0.105	0.100
Eta	0.841	0.118	-0.230	0.431
Epsilon	-0.625	-0.095	0.014	0.537

Table 5. Group centroids in discriminant space

	D 1	D 2	D 3	D 4
ND	0.254	-0.126	-0.127	-0.019
AL	-0.860	0.528	0.463	-0.166
BP	-1.702	0.967	1.049	0.137
EP	-1.121	0.865	0.445	0.302
IO	-0.655	0.217	0.160	0.051
NN	-2.184	0.553	0.810	0.163
NE	-0.891	0.194	0.486	0.064
DA	-0.615	0.475	-0.060	-0.046
OD	-0.654	-0.222	0.480	-0.329
PT	-1.117	1.126	0.663	-0.186
SC	-0.983	0.544	-0.495	0.498
PS	-1.383	0.753	0.978	0.158

Table 6. Canonical correlation coefficients

	Sigma	Chi	Delta	Eta	Epsilon
Alpha	0.74	0.79	0.72	0.77	0.61
Sigma		0.76	0.72	0.74	0.64
Chi			0.85	0.86	0.57
Delta				0.86	0.56
Eta					0.59

DISCUSSION

Canonical correlation coefficients between the scores on the individual scales are medium high. It is particularly interesting structure and number (on average about 10) of significant canonical correlation factors which implies an extremely complex relationship between reactions at all scales. It is a result which indirectly confirms extremely complex relationship of conative regulatory systems which is foreseen by cybernetic theory of personality, on the basis of which are incurred these measuring instruments.

CONCLUSIONS

Results from earlier studies are replicated on a much larger sample:

- Metric characteristics of scales are very good, as in previous studies;
- Similar structure of polar taxons was found;
- Discrimination between healthy subjects ad those with psychiatric diagnoses was successful.

Canonical correlation analysis showed interconnection of reactions on certain scales and extremely complex relationship between them which indirectly confirms the theoretical model on the basis of which the scales are formed.

The usefulness of this scales is confirmed in the clinical setting and in the selection of candidates for employment.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 513-519 *Original paper*

NURSING EVALUATION OF DIABETES SELF-MANAGEMENT IN TERTIARY HEALTHCARE SETTINGS IN CROATIA

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SUMMARY

Background: *Systematic and efficient education on patient self-management behaviour represents one of the key approaches to diabetes treatment. The aim of this paper was to evaluate the current process and content of nursing assessment of illness self-management behaviour in persons with diabetes treated at a tertiary healthcare facility.*

Subjects and methods: *Electronic patient records of N=15,116 persons with type 2 diabetes (51.3% men) who took part in nursing evaluation and education throughout 2011 were collected. The patients' mean age was 65.0±11.1 years, with mean diabetes duration of 12.6±8.3 years; they were mostly treated with oral anti-diabetic drugs (38.4%) or insulin therapy (38.5%). The likelihood of non-participation in the nursing evaluation was predicted based on a number of patient characteristics using a multivariate logistic regression.*

Results: *The nurses mostly rated the patients' self-management knowledge and real-life application of that knowledge as appropriate; however, in a large number of patients, the nursing evaluation was not evidenced in the electronic patient record. Multivariate logistic regression revealed that longer diabetes duration, insulin treatment and better glyceamic control as measured by glycated haemoglobin were associated with a higher likelihood of participating in a nursing evaluation and diabetes re-education.*

Conclusion: *Diabetes specialist nurses may use informal criteria when deciding which type 2 diabetes patients to interview about diabetes knowledge and self-care. Participative research on the processes of nurses' decision-making may be needed.*

Key words: *diabetes mellitus - type 2 - patient education as topic - self-care*

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INTRODUCTION

Patient education of persons with diabetes is one of the primary tasks of their healthcare teams, and the goal of this process is to achieve and maintain the patients' independence, competence and self-efficacy in managing their illness. Chronic illness self-management education has a long-lasting tradition. Nevertheless, traditional models of patient education can hardly fit into the model of chronic care seen as a partnership between the healthcare team and the patient, which has led to novel approaches to patient education. Traditional patient education models mostly teach facts about the disease and elaborate the technical aspects of self-management, with the assumption that knowledge (seen as the amount of information that a patient has) is sufficient in motivating a patient to alter their health-related behaviour. This approach to patient education corresponds to a paradigm that views the physician as the only person in charge of evaluating the success or failure of chronic illness treatment, while the patient's task is to comply as fully as possible with the physician's recommendations. As opposed to the traditional, compliance-oriented approach, patient education targeted at self-management competencies and skills entails teaching problem-solving skills, and is driven by those disease-related issues that the patient perceives as personally relevant. The rationale behind such an educational approach is that the way to achieve better disease control is to increase the patient's self-efficacy in managing the disease.

One of frequently studied outcomes of patient education is the patients' knowledge on the disease and its treatment. Meta-analyses have shown that patient education does indeed increase the patients' knowledge (Deakin et al. 2005, Loveman et al. 2003, Norris et al. 2002a), but that those changes do not correlate with changes in glycated haemoglobin (HbA1c) values (Loveman et al. 2003). This lack of correlation demonstrates that even though knowledge is necessary, it alone is insufficient in achieving optimal disease regulation – which is in disagreement with the assumptions underlying the traditional model of diabetes education. Although the number of studies that analysed disease self-management as an educational outcome is modest, it seems that similar results have been found: even though patient education increases the frequency of blood glucose self-measurements, this does not correlate with changes in HbA1c. Nevertheless, analyses of randomized controlled trials have shown an overall impact of diabetes education in lowering HbA1c: clinically significantly larger improvements in HbA1c were found in patients who were assigned to self-management education programs, as compared to patients who were randomized to control groups with no diabetes education. However, the impact of patient education on glycated haemoglobin seems to be transient, as these inter-group differences are consistently found only over

fairly short, 3-month follow-up intervals (Loveman et al. 2003, Norris et al. 2002a, Norris et al. 2002b, Ellis et al. 2004).

Literature reviews and meta-regressions have identified some of the characteristics of the educational interventions that are likely to be more successful (Norris et al. 2002b, Ellis et al. 2004, Glazier et al. 2006). Interactive interventions, especially those that include cognitive restructuring seem to be more successful than other types of educational interventions, in particular those didactic in nature. From the organisational standpoint, interventions that are implemented face-to-face are delivered by interdisciplinary education teams, that include a greater number of sessions, and that have longer total duration of patient-educator contact, seem to be more efficient in lowering HbA1c compared to other educational interventions. Finally, literature reviews have shown that, when working with socially vulnerable patient populations, who are at a higher risk of poor glycaemic control, interventions should be individually tailored, adjusted to the patient's cultural context, and directed towards achieving high disease management self-efficacy. Of note, a recent meta-analysis (Sigurdardottir et al. 2007) has failed to demonstrate that the methods and the content of patient education, or the duration of patient-educator interaction, are predictors of HbA1c lowering. However, this might be attributed to the fact that single-session didactic interventions are no longer implemented as widely as before. When predicting and evaluating the impact of patient education on lowering HbA1c, patient characteristics should be taken into account. Most importantly, patient education has been shown most effective in patients with poor glycaemic control, while its impact is considerably smaller in persons with good glycaemic regulation, partly due to ceiling effects (Duke et al. 2009).

Studies that examined the clinical outcomes of diabetes treatment – the incidence of chronic complications and mortality rates – are very few. Interventions that included these endpoints have not found differences in the incidence of foot ulcers or retinopathy mortality rates between educational and control groups, possibly because they included follow-up periods of only one year (Deakin et al. 2005).

This study aimed at gaining insight into the results of a nursing evaluation of persons with diabetes treated at a tertiary healthcare facility. From the expert and practical standpoint, the results of this research could provide data that substantiate the need for changing the existing nursing evaluation model so as to make it more suitable for a wider range of patient populations.

This study examined two research problems. The first was the frequency of nursing evaluation of diabetes patients' knowledge on disease self-management, the application of that knowledge and obstacles to its application. It was hypothesised that the nursing evaluation of patients' knowledge on the self-management of the disease, the patients' application of that knowledge and obstacles to its application, shall differ based on the type of disease self-management behaviour. The second issue of concern was the differences in socioeconomic and diabetes-related characteristics between patients who participated and did not participate in the nursing evaluation. The assumption was that patients with shorter diabetes duration, those with poorer glycaemic control and persons treated by insulin would be more likely to be included in the nursing evaluation than persons with longer diabetes duration, those with better glycaemic control and treated by oral anti-diabetic drugs.

SUBJECTS AND METHODS

Study protocol

Data used in this research were gathered during the course of the regular nursing evaluation of diabetes self-management that takes place as an integral part of control visits scheduled on the premises of Vuk Vrhovac University Clinic. Such an evaluation is carried out through a patient interview that concerns the following disease self-management aspects: compliance with the appropriate dietary regimen, physical activity, foot care, appropriate insulin self-administration, blood glucose self-measurement, and the ability to recognise hypoglycaemia and respond to it in a proper and timely manner.

Regarding dietary regimen, the nursing evaluation assessed whether the patient understands the importance of an appropriate diabetes-tailored healthy diet and the impact of the type of foodstuffs and the manner of food preparation on blood sugar levels. The survey on physical activity identified whether the patient is familiar with the therapeutic importance of regular exercise and with the principles of harmonisation of physical activity, diet and blood sugar levels. The foot care survey evaluated whether the patient understands the importance of proper foot care in persons with diabetes, is familiar with the appropriate foot care and protection techniques, and applies these techniques in everyday life. In persons who were treated by insulin, the nurses evaluated whether the patient understands the principles of insulin action, their knowledge on adjusting insulin doses based on blood sugar levels, diet and physical activity, the appropriateness of their insulin self-injection technique, and their capability to recognize and manage hypoglycaemia. Finally, in evaluating blood sugar self-measurement, nurses assessed whether the patient understands the importance of regular glycaemia self-control, implements the knowledge in daily life, suitably responds to the measurement results, and uses the self-measurement device in a technically appropriate way.

Nurses used a semi-structured clinical nursing interview to assess three aspects of patient self-management capabilities: 1) information/knowledge on the topic; 2) application of that knowledge; and 3) reasons behind the inadequate application of that knowledge (when applicable). The degree of information on the topic was

registered as either satisfactory or unsatisfactory. In cases where the interviewing nurse assessed patient's knowledge on the topic as unsatisfactory, the patient was re-educated so as to increase his or her knowledge on the relevant disease-related topic. In the next step, the nurse evaluated the degree in which a patient applies the knowledge. In evaluating adherence to proper diet, foot care, insulin self-administration and blood glucose self-measurement, the interviewing nurse recorded the results in the following categories: "applied regularly by the patient"; "applied incorrectly by the patient"; "applied irregularly by the patient", or "not applied by the patient at all". Regarding patients' physical activity, the ranking read as follows: "extremely rare physical activity", "irregular physical activity"; "moderate physical activity", or "demanding physical activity 2-3 times a week", with the last two categories perceived as satisfactory answers. Recognition of and responding to hypoglycaemia was categorised as: "no hypoglycaemia episodes at all"; "hypoglycaemia recognised and responded to in an appropriate and timely manner"; hypoglycaemia recognised, but not responded to in an appropriate and timely manner"; "hypoglycaemia not recognised nor responded to". In cases where the interviewing nurse established that the patient lacked knowledge about a certain aspect self-management or implemented it inappropriately (improperly or irregularly), she registered the reasons behind such patient's behaviour. The possible reasons for the lack of or improper disease self-management were: "emotional hindrances/stress", "incorrect health beliefs", "lack of information", "lack of support", and "inadequate personal engagement". When explaining the reasons behind their lack of/inadequate physical activity, patients could also opt for physical disability as the main reason.

The patient sample included in the study was composed of every person with type 2 diabetes entered into the CroDiab Net electronic database (Poljičanin et al. 2005) maintained by Vuk Vrhovac University Clinic. Upon the approval of the Registry administrator, socio-demographic data (gender, age), data on diabetes (duration of the disease, type of therapy (diet only, oral hypoglycaemic drugs, insulin, combined insulin plus oral hypoglycaemic drug treatment), data on body mass index (BMI), data on glycated haemoglobin (HbA1c) levels and the data on nursing evaluation above elaborated were gathered.

The study sample comprised a total of 15,116 persons (out of which 7,761 men and 7,355 women; χ^2=10.905, p<0.001) with type 2 diabetes, who attended a control visit at the Vuk Vrhovac University Clinic throughout 2011. A majority of these patients participated in the nursing evaluation (N=10,307; response rate 68.2%). The patients in the sample were aged 65.0±11.08 years on average, with the average diabetes duration of 12.59±8.31 years. The vast majority of the patients were treated with oral hypoglycaemic drugs (38.4%), followed by those insulin-treated (21.3%) and those treated by a combination of insulin and oral hypoglycaemic agents (17.2%), while the representation of the persons treated exclusively by diabetic diet was negligible (0.3%). Glycaemic control, as measured by glycated haemoglobin was 7.4±1.19% on average, while their body weight was established to be above the recommended (BMI=29.5±4.53 kg/m^2) (Table 1).

Table 1. Descriptive sample data

	N (%)	M	SD
Age	15,116 (100)	65.0	11.08
Diabetes duration	8,109 (53.6)	12.6	8.31
Body Mass Index	13,139 (86.9)	29.5	4.53
HbA1c	13,193 (87.3)	7.4	1.19
Type of therapy			
diet	42 (0.3)		
OHD	5,802 (38.4)		
insulin and OHD	2,597 (17.2)		
insulin	3,219 (21.3)		
unknown	3,456 (22.9)		

OHD = oral hypoglycaemic drugs

Table 2. Nursing evaluation of patient knowledge on various disease self-management behaviours

	Sufficiently informed N (%)	Insufficiently informed N (%)	Not assessed N (%)
Proper diet	10,224 (67.2)	50 (0.3)	4,842 (32.0)
Physical activity	7,590 (50.2)	19 (0.1)	7,507 (49.7)
Foot care	3,996 (26.4)	16 (0.1)	11,104 (73.5)
Self-control BG*	4,185 (72.0)	5 (0.1)	1,626 (28.0)
Insulin self-administration*	3,403 (58.5)	5 (0.1)	2,408 (41.4)
Hypoglycaemia*	3,432 (59.0)	7 (0.1)	2,377 (40.9)

BG = blood glucose; * Only data on insulin-treated patients have been included

Data Analysis

Descriptive data were presented as frequencies and percent shares for categorical variables, while arithmetic means and standard deviations were calculated for continuous variables. Differences between categorical variables were calculated using the chi-square test, while the differences between continuous variables were calculated using the *t*-test. The likelihood of participation or non-participation in the nursing evaluation was predicted based on a number of patient characteristics using multivariate logistic regression.

The statistical significance level was set at $p<0.05$ in all analyses. Statistical analyses were made using SPSS 16.0 Software.

RESULTS

Knowledge of disease self-management, application of that knowledge and possible hindrances to its application

Knowledge related to diet was evaluated in roughly two-thirds (67.5%) of the patients; information on physical activity were evaluated in roughly one-half (50.3%) of them; while the share of patients evaluated for their knowledge on appropriate foot care was only about one-quarter (26.5%) (Table 2). Data on the level of information on blood glucose self-measurement practices, self-administration of insulin and hypoglycaemia self-management were gathered only in insulin-treated patients (N=5,816). Judging by the obtained data, all of these self-management behaviours were assessed in over one-half of the patients, with the blood glucose self-monitoring being the subject of the nursing evaluation in the relatively highest number of patients on insulin therapy (72.1%). Virtually all patients that took part in the evaluation were assessed as sufficiently informed about disease self-management behaviours.

Table 3 displays the appropriateness of the application of patients' knowledge of disease-tailored diet, foot care, blood glucose self-control, and insulin self-administration. Less than one-half of the patients were deemed to comply with an appropriate diet (48.6%), while the behaviour was not evaluated in nearly one-third (32.3%) of the patients. Among those who inconsistently follow the appropriate diet, the vast majority is represented by those who adhered to it sporadically. Blood glucose self-control was estimated in the majority of insulin-treated patients (although over one-quarter of that subsample remained unevaluated), who were mostly (68.1%) assessed to adequately perform blood glucose self-control. The appropriateness of insulin self-administration was neglected to be evaluated in almost one-half (41.5%) of the patients on insulin therapy. In those who were evaluated in that regard, the nurses assessed most patients as knowledgeable about the proper insulin self-administration.

Data on physical activity evaluation revealed that the behaviour was not evaluated in nearly one-half of the patients (N=7,550, 49.9%). As for the evaluated patient pool, 6,458 (42.7%) of them had been assessed as moderately physically active, while a regimen of vigorous physical activity 2-3 times a week was recorded in 256 (1.7%) of them. The remaining evaluated patients were physically active either sporadically (n=535, 3.5%) or extremely rarely (n=317, 2.1%).

Table 3. Assessment of the frequency of disease self-management practices

	Performed regularly N (%)	Performed inappropriately N (%)	Performed sporadically N (%)	Not performed N (%)	Not assessed N (%)
Diet	7,349 (48.62)	881 (5.83)	1,740 (11.51)	265 (1.75)	4,881 (32.29)
Foot care	3,914 (25.89)	0 (0)	3 (0.02)	1 (0.01)	11,198 (74.08)
Self-control*	3,958 (68.05)	36 (0.62)	174 (2.99)	17 (0.29)	1,631 (28.04)
Insulin*	3,282 (56.43)	19 (0.33)	101 (1.74)	2 (0.03)	2,412 (41.47)

* Only data on insulin-treated patients have been included

Table 4. Nursing evaluation of reasons behind non-application of various aspects of disease self-management knowledge

	Not assessed	Physical limitations	Incorrect health beliefs	Insufficient support	Insufficient personal engagement	Lack of information	Psychological issues
Proper diet	1,002	N/A	107	95	1,533	28	121
Physical activity	323	463	4	3	59	0	0
Foot inspection	3	N/A	0	1	0	0	0
Insulin self-administration	109	N/A	2	3	5	3	0
BG self-measurement	124	N/A	8	11	70	3	11
Hypoglycaemia	100	N/A	0	0	0	0	0

BG = blood glucose

The appropriateness of patients' response to hypoglycaemia episodes was not evaluated in 41.1% of insulin-treated patients (n=2,389). The remaining 41.3% of patients (n=2,402) were deemed to recognise their hypoglycaemia and respond to it in a proper and timely manner, while 15.9% (n=925) of eligible patients had not experienced symptoms or signs of hypoglycaemia. Forty-four patients (0.8%) failed to recognise hypoglycaemic episodes, while 56 (1%) were assessed to respond in an inadequate manner.

The frequencies of reasons recorded by nurses as the causes of inadequate diabetes self-management are displayed in Table 4. The reasons behind the non-compliance with the appropriate diet and those behind the negligence to exercise on a regular basis were recorded in 65.3% and 62.1% of patients, respectively. The predominant reason for diabetes diet non-adherence, as assessed by the nurses, was inadequate personal involvement (recorded in 53.1% of the eligible patients), while the main reason for physical inactivity was physical disability (recorded in 54.3% of the patients). The appropriateness of foot care was assessed in only 4 patients, which precluded a meaningful analysis of the reasons for the non-application of knowledge on foot care. Among the self-management aspects specific for insulin-based therapy, most of the interviewed patients (45.4%) were evaluated for the regularity of their blood glucose self-measurement; the nurses attributed non-compliance most commonly to inadequate personal involvement (30.8% of the patients). The number of patients in which the reasons behind inadequate insulin self-administration had been sought was too low to be meaningfully analysed (n=13), while the reasons behind the inadequate response to hypoglycaemia failed to be recorded in any of the patients.

Comparison between the patients who did and who did not take part in nursing evaluation

Testing of differences in socio-demographic characteristics of persons who did and those who did not take part in nursing evaluation, revealed that older patients (t=-11.40, p<0.001) were more likely to take part in the evaluation in reference, while gender differences between the participants and non-participants were not statistically significant (χ^2=1.093, p=0.303). With respect to disease characteristics, nursing evaluation was more commonly performed in insulin-treated participants than in patients on oral hypoglycaemic drugs (χ^2=47.033, p<0.001). Participants and non-participants did not differ in disease duration, body mass index and glycated haemoglobin values (Table 5).

A multivariate logistic regression model revealed that patients who were included and who were not included in the nursing evaluation differed in diabetes duration, type of therapy and glycaemic control (Table 6). Patients with longer diabetes duration were more likely to be included in the nursing evaluation and education, with the likelihood of participation rising by 1% per year of illness (OR=1.01, 95% CI=1.00-1.02, p=0.010).

Table 5. Comparison between patients who were and who were not included in the evaluation

	Included		Not included			
	M (N)	SD	M (N)	SD	t (χ^2)	p
Age	65.5	10.10	63.5	12.82	-11.396	<0.001
Disease duration	12.5	7.96	12.8	8.92	1.608	0.108
BMI	29.5	4.48	29.6	4.72	1.465	0.143
HbA1c	7.4	1.16	7.4	1.29	-0.200	0.841
Gender						
male	(5262)		(2,499)		(1.093)	0.296
female	(5045)		(2,310)			
Therapy*						
OHD	(4,297)		(1,505)		(47.03)	<0.001
insulin	(4,620)		(1,196)			

BMI = body mass index; OHD = oral hypoglyecemic drugs; * Due to their small number, diet-only patients were excluded from the study, while those on combined OHD + insulin therapy were included into the insulin-treated group

Table 6. Multivariate model of differences between participating and non-participating patients

	OR	95% C.I.		p
		Lower	Upper	
Gender (male=1)	1.01	0.89	1.15	0.847
Age	1.00	0.99	1.01	0.870
Body Mass Index	0.99	0.98	1.01	0.312
HbA1c	0.93	0.89	0.98	0.011
Type of therapy (insulin=1)*	0.75	0.65	0.87	<0.001
Diabetes duration	1.01	1.00	1.02	0.010

* Due to their small number, diet-only patients were excluded from the study, while those on combined OHD + insulin therapy were included into the insulin-treated group

Furthermore, patients treated with oral hypoglycaemic drugs were established to be 25% less likely to take part in the nursing evaluation than insulin-treated patients (OR=0.75, 95% CI=0.65-0.87, p<0.001). Finally, patients with higher glycated haemoglobin values were less likely to participate in nursing evaluation as compared to those having lower HbA1c values (OR=0.93, 95% CI=0.89-0.98, p=0.011). Each 1% rise in glycated haemoglobin values lowered the chance of patient participation in nursing evaluation by 7%.

DISCUSSION

Data has shown that the majority of patients were assessed to be well informed and knowledgeable on diabetes self-management behaviours; a lack of disease-related information and knowledge was recorded in only 0.1-0.3% of the patients who participated in the evaluation.

This study strived to assess the regularity of self-management practices in patients established to be sufficiently knowledgeable about their disease. The nurses assessed that the interviewed patients typically performed self-care behaviours with adequate regularity. Although this might be true, one cannot dismiss the possibility that these results are a consequence of insufficient specificity of measurement and/or recording tools used for patient self-management evaluation. In view of that, future clinical research should attempt to validate the evaluation criteria and methodology employed that nurses use in assessing patient diabetes self-management practices. For instance, semi-structured interview schedules with open-ended questions might turn out to be more informative than the ones currently in use.

The study results show that nursing evaluation and education is far more likely to include patients with a longer duration of diabetes; in fact, the likelihood including a patient into the evaluation and re-education process rises by 1% per year of illness. Similarly, patients taking oral hypoglycaemic drugs are 25% less likely to participate in nursing evaluation compared to those on insulin. These results partly reveal the criteria driving the decisions on patient education priorities taken by nurses in understaffed facilities. It appears therefore that precedence in nursing evaluation and education might be given to persons who have a need for a more detailed education, due to their more complex therapy or to chronic disease complications that are more likely in patients with longer illness duration.

A possible limitation of this study lies in the fact that the knowledge on various self-management behaviours was not assessed, i.e. recorded at all, in a considerable percentage of interviewed patients. For instance, 32% of patients were not evaluated for the appropriateness and regularity of their disease-tailored diet, and 73% of patients were not evaluated for their knowledge on proper foot care.

The results of this study are possibly limited also by the fact that data were collected in only one institution, the only tertiary diabetes clinic in Croatia. For this reason, it is impossible to exclude potential organization-level sources of bias (e.g., nurses' practices in evaluating diabetes knowledge and self-care may be a reflection of specific conditions in this institution), and to generalize the results to other levels of diabetes care (e.g. primary care).

CONCLUSIONS

These results point towards two possible areas of improvement in the implementation and recording of regular nursing evaluations of patients with diabetes. First, even the patients assessed to have sufficient knowledge about their disease are likely to vary considerably in the degree of that knowledge, but the existent, binary format of recording evaluation outcomes is not able to reflect that. Therefore, future efforts should be targeted at establishing a more detailed and more substantial standard of minimum patient knowledge to be considered sufficient in a nursing evaluation. Such standards also need to accommodate for the needs and limitations of individual patients who participate in a nursing evaluation and re-education. The second important area of improvement lies in the fact that a considerable number of patients were not evaluated for their knowledge on specific self-management behaviours, especially regarding foot care. A possible reason for this situation might be the work overload of the nurses who must decide on the target evaluation and patient re-education area on a case-by-case basis. It is therefore possible that nurses consider some of the self-care behaviours (e.g., diet) a higher priority than other behaviours (e.g. foot care). Therefore, future clinical research should attempt to identify the rationales underpinning healthcare professionals' decisions on patient education priorities. On an operational level, alternative education modalities that would allow for a more detailed patient education on certain self-management practices (such as foot care) should be explored and tested for their efficiency (for instance, the possibility of community nursing services involvement), taking thereby into account limitations to patient education arising from an everyday work overload.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 520-527 *Original paper*

THE MOST COMMON FACTORS INFLUENCING ON QUALITY OF LIFE OF THYROID CANCER PATIENTS AFTER THYROID HORMONE WITHDRAWAL

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SUMMARY

Background: *The aim of study was to evaluate which factors impact mostly on life-quality of patients with differentiated thyroid carcinoma after thyroid hormone withdrawal.*

Subjects and methods*: 150 patients were enrolled in the study by using Quality of life- Thyroid version questionnaire in which they expressed their physical, psychological, social and spiritual well-being. The answers have been interpreted on a scale from 0 to 10. All patients underwent four weeks levothyroxine withdrawal in preparation for I-131 procedures and thyroglobulin testing.*

Results: *Individual statements on the physical subscale showed that patients had most difficulties with fatigue, intolerance to cold and heat, sleep changes and weight gain, but with higher average values than expected. Fatigue was one of the most common physical difficulties. Female patients had significantly more difficulties than male respondents. Five most expressed psychological difficulties have been stress caused by initial diagnosis, followed by stress caused by surgical treatment, fear of metastases, stress caused by initial radioiodine ablation treatment and fear of cancer recurrence. Generally, results revealed troubles mostly in physical symptoms relating to thyroid hormone withdrawal, as well as psychological distress caused by initial diagnosis. Respondents with higher educational level achieved a significantly higher score than less educated patients (p=0.026, Mann-Whitney U test). Illness was very distressing for their families (median value 1, range: 0 to 10) and they reported insufficient support from others (1, range: 0 to 10), but they did not feel isolated. Family and work consequences were less apparent.*

Conclusion*: The results of QOL-Thyroid questionnaire help to identify high-risk areas in patients' lives that are negatively affected by hormone withdrawal. Regarding the wide definition of quality of life, a positive impact on patients' recovery could be achieved by directing attention to most expressed difficulties noted in this questionnaire.*

Key words: *quality of life - differentiated thyroid carcinoma - thyroid hormone withdrawal - questionnaire*

* * * * *

INTRODUCTION

Increase of thyroid carcinoma incidence and favorable prognosis after treatment raised attention on quality of life (QOL) as an important part of patients' recovery (Dean & Hay 2000). Differentiated thyroid carcinomas (DTC) originate from follicular thyroid cells, and include papillary and follicular carcinoma and their variants. Their proportion is in majority, in the range of 70 to 90% (Mc Dougall & Berry 2006). Generally, patients with these types of carcinomas have a large survival rate of about 91% for the entire DTC group, although male patients, patients older than 45 years with unfavorable histology and larger tumor with exstracapsular spread or distant metastases have a poorer prognosis (Almeida et al. 2009, Fahey et al. 1995, Pacini et al. 2010). Better screening methods are probably the reason for higher incidence of thyroid cancer, especially micropapillary carcinoma. Improved diagnostic procedures such as neck ultrasound followed by fine-needle aspiration biopsy of suspicious lesions make the possibility of early detection of thyroid malignancy as well as neck lymph node metastases (Nix et al. 2005). After initial diagnosis patients undergo total thyroidectomy usually followed by radioiodine ablation of remnant tissue. Those initial treatment decreases the risk of recurrence by therapeutic effect on possible micrometastases, increases the sensitivity of serum thyroglobulin testing because the thyroid remnant tissue is a potential source of thyroglobulin and increases the sensitivity of further whole-body scanning as it removes residual functioning thyroid tissue (Pacini et al. 2010, Nix et al. 2005). Thyroid stimulating hormone (TSH) suppression after initial treatment is performed with levothyroxine to avoid pituitary gland to produce TSH which stimulates thyroid follicular cells, and, in that way, suppress the growth of any remaining thyroid cells (Nix et al. 2005). But, patients are periodically monitored for thyroid cancer recurrence with blood tests thyroglobulin measurement, I-131 whole body scan and neck ultrasound. As the sufficient TSH level (more than 30 mU/L) has an important role in radioiodine uptake and thyroglobulin secretion, patients should undergo four weeks L- thyroxine withdrawal in order to increase the successfulness of radioiodine ablation as well as sensitivity in searching for metastases. Those TSH production after thyroid hormone withdrawal leads to hypothyroid state that is associated with the serious side effects on physical, psychological and social aspects which can have a negative impact on the patient's quality of life

(QOL) (Wang et al. 2010). The one way to avoid these difficulties is application of recombinant TSH (rhTSH) that is justified, especially in older patients with chronic diseases, in patients who cannot achieve sufficient level of serum TSH and in ablation of remnants in low risk patients (Wang et al. 2010), but because of relatively high price its use is limited and sometimes not under reimbursement policy of health insurance.

The aim of this study was to measure QOL in DTC patients who undergo LT4 withdrawal due to clinical follow-up or in recently operated patients before radioiodine ablation. The study was made to identify which factors impact mostly on QOL in order to pay attention to noted signs with a purpose of improving patients' recovery.

SUBJECTS AND METHODS

Study Sample

The study included all thyroid cancer patients submitted for diagnostic or therapeutic radioiodine administration under thyroid hormone withdrawal to Clinical Department of Nuclear Medicine from September 2010 to April 2011. Out of 162 eligible patients, 158 (97.5%) agreed to participate in the study. Data from 8 of 158 participants (5%) had to be discarded because of incomplete responses. Thus, 150 patients were enrolled in the study (response rate 92.5 %). All patients underwent four weeks levothyroxine withdrawal before entering the study. 125 patients (83.3%) were in a periodical follow-up and 25 (16.7%) were recently surgically treated. Patients which have been submitted to hospital because of follow up received 185 MBq (5mCi) of I-131 as a diagnostic dose, while recently surgically treated patients received from 888MBq (24 mCi) to 3700 MBq (100 mCi) for thyroid remnant ablation. All applied procedures are part of routine diagnostic and therapeutic protocols that have been approved by the authorities. The study was approved by the institutional ethic committee and each patient signed an informed consent.

Questionnaire

Research is performed by using Quality of life - Thyroid version (QOLTV) questionnaire, which has been developed and recommended for future use by the City of Hope National medical center and Beckman Research Institute (Duarte, California, United States), which is the part of the United States National Cancer Institute especially designed to measure quality of life of differentiated thyroid carcinoma patients (Ferrell et al. 1995). The thyroid version was adapted from a form created for use in the general population of cancer survivors. The questionnaire consists of 56 statements divided into four subscales related to physical (PHWB), psychological (PSYWB), social (SOCWB) and spiritual well being (SPWB). The answers are numbered on a scale from 0 to 10 with word anchors at each end of the scale. The answers are interpreted in a way that 0 means the worst outcome, and 10 mean the best outcome. Some answers have reverse order, so during the evaluation of results we had to switch the result by subtraction from number 10. We analyzed the statements individually and also as a composite score of physical, psychological, social and spiritual well-being. The questionnaire demonstrated good internal consistency; Cronbach α of the overall scale was 0.92. Subscale alphas ranged from 0.58 for spiritual well being, 0.82 for physical, 0.84 for social and 0.90 for psychological well being. The original English version of the questionnaire was translated into Croatian language to facilitate understanding of the questions for our patients. The patients completed the questionnaire after detailed explanation how to fulfill it and were given sufficient time to resolve dilemmas about the questionnaire. The patient was asked to read each question and then circle a number on a scale between 0 and 10 to show a level of agreement or disagreement with the statement during the period of hypothyroidism, with special emphasis on the last week of thyroxine withdrawal.

The questionnaire was completely anonymous. Patients had designation code in order to statistically process their data.

Demographic data included age, sex and education level.

Serum TSH concentration was determined at the time of completion of the questionnaire and all patients were hypothyroid with TSH values greater than 30 mIU/L (normal range 0.4-4.2 mIU/L). According to TSH level patients were divided into 3 groups: TSH level between 30 to 60 mIU/L (34 patients), 61-100 mIU/L (71 patients), and >100 mIU/L (53 patients).

According to education level patients were divided into two groups. First group included respondents with secondary education, and second group included tertiary (undergraduate and postgraduate) educated respondents.

Statistics

Cronbach's α was used as a measure of internal consistency, based on the average inter-item correlation for all questions and for statements related to physical, psychological, social and spiritual well being. Pearson's chi-square exact test, Mann-Whitney U-test or Kruskal-Wallis rank test, or simple linear regression were used for different comparisons in our bivariate analysis. All reported tests are two-sided.

Multivariate analysis was done by multiple linear regression for the physical, psychological, social and spiritual well being score as dependent variables respectively. Initially variables with a $p<0.25$ on bivariate analysis were included in the model. There were no serious violations of the assumptions of linearity, normality of residuals, homoscedasticity and

no evidence of collinearity in our multivariate linear regression model. The statistical analysis was performed by STATA/IC ver.11.1. (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP). Results of two-sided statistical tests in which P values were less than 0.05 were considered to be statistically significant.

RESULTS

A total of 150 patients (24.0 % male) were included in the study (response rate 92.5 %). The median age was 53 (range: 18 to 87) years. There was no statistically significant difference between sex regarding age (p=0.30, Kruskall-Wallis, d.f. 2). The socio-demographic data, clinical features and self-reported data are detailed in Table 1.

The median physical well being score was 78 (range: 26 to 127) out of maximum 130 points. Male respondents achieved a significantly higher score than female patients (median: 89, range 40 to 124 vs. 72.5, range 26 to 127; p=0.005, Mann-Whitney U test) (Table 2). There were no statistically significant differences in PHWB score between groups with different TSH level, educational level, between patients in follow-up and nearly operated patients, and regarding age. Mean TSH value ± SD in the group was 82.5±37.6 mIU/L (normal range 0.4-4.2 mIU/L).

The analysis of patients' individual statements on the PHWB subscale (Table 3) showed that they had most difficulties with fatigue (4, range: 0 to 10), intolerance to cold and heat (5, range: 0 to 10), sleep changes (5, range: 0 to 10) and weight gain (5, range: 0 to 10) (Table 2). Female patients had significantly more difficulties than male respondents with the following symptoms: fatigue (4, range: 0 to 10 vs 6, range 0 to 10; p=0.033, Mann-Whitney U test), appetite changes (7, range: 0 to 10 vs 9, range 2 to 10; p=0.034, Mann-Whitney U test), sleep changes (5, range: 0 to 10 vs 6, range 1 to 10; p=0.039, Mann-Whitney U test), dry skin or hair changes (4, range: 0 to 10 vs 9, range 2 to 10; p<0.001, Mann-Whitney U test), voice changes (6, range: 0 to 10 vs 9.5, range 3 to 10; p<0.001, Mann-Whitney U test), swelling/ fluid retention (5, range: 0 to 10 vs 9, range 1 to 10; p<0.001, Mann-Whitney U test), but less with tolerance to cold and heat (6, range: 0 to 10 vs 3.5, range 1 to 10; p=0.032, Mann-Whitney U test).

Table 1. Demographic, clinical features and self-reported data

	Number (%)	Median (range)
Age (year)		53 (18-87)
Gender		
Male	36 (24)	
Female	114 (76)	
Educational level		
Secondary education	112 (74.7)	
Tertiary	38 (25.3)	
Follow-up	125 (83.3)	
Ablation	25 (16.7)	
TSH (mIU/L)		
30 to 60	33 (22)	
61-100	66 (44)	
>100	51 (34)	
QOLTV*		
Physical WB** (0-130)		78 (26-127)
Psychological WB (0-220)		107 (41-199)
Social WB (0-140)		78.5 (20-129)
Spiritual WB (0-70)		38 (10-70)

*QOLTV - Quality of life - Thyroid version; **WB - well being

Table 2. Comparison of thyroid patients well being by age, gender, way of radioiodine aplication,education and TSH level

Variables	No. of patients	Physical well being Median (range)	P	Psychological well being Median (range)	P	Social well being Median (range)	P	Spiritual well being Median (range)	P
Age*									
<40	27	77 (43-122)	0.45	114 (53-199)	0.36	89 (50-129)	0.23	41 (10-70)	0.49
40-60	81	79 (26-124)		102 (41-199)		77 (21-125)		39 (13-64)	
>60	42	70 (33-127)		111 (54-199)		76 (20-120)		37 (14-65)	
Gender†									
Male	36	89 (40-124)		119 (59-199)		82.5 (43-129)		35 (13-60)	
Female	114	72.5 (26-127)	0.005	103.5 (41-199)	0.06	77 (20-125)	0.10	39.5 (10-70)	0.41
Follow-up†	125	78 (26-127)		107 (41-199)		80 (21-129)		39 (10-70)	
Radioablation†	25	79 (33-124)	0.52	106 (71-197)	0.77	73 (20-120)	0.25	36 (18-65)	0.62
Educational level†									
Secondary	112	76 (26-127)		105 (41-199)		78 (20-125)		38 (13-65)	0.54
Tertiary	38	83 (41-122)	0.12	113 (51-199)	0.11	81.5 (21-129)	0.026	40 (10-70)	
TSH (mIU/L)*									
30 to 60	33	71 (26-122)	0.28	106 (49-199)	0.71	81 (35-123)	0.72	41 (21-70)	0.12
61-100	66	77 (32-124)		102.5 (41-197)		75 (20-125)		36 (10-65)	
>100	51	80 (40-127)		112 (51-199)		82 (21-129)		40 (13-60)	

*Comparison of patients well being score; Kruskal-Wallis rank test; †Comparison of patients well being score; Mann-Whitney U-test

Table 3. Physical, psychological, social and spiritual symptoms tests during levothyroxine withdrawal in patients with thyroid carcinoma by sex

Statement	All patients (n=150) Median (range)	Male (n=36) Median (range)	Female (n=114) Median (range)	P value*
Physical well being	78 (26-127)	89 (40-124)	72.5 (26-127)	0.005
Fatigue	4 (0-10)	6 (0-10)	4 (0-10)	0.033
Appetite changes	7 (0-10)	9 (2-10)	7 (0-10)	0.034
Aches or pain	9 (0-10)	9 (1-10)	8 (0-10)	NS
Sleep changes	5 (0-10)	6 (1-10)	5 (0-10)	0.039
Constipation	10 (0-10)	10 (1-10)	9 (0-10)	NS
Menstrual changes or fertility	10 (0-10)		10 (0-10)	NS
Weight gain	5 (0-10)	7 (0-10)	5 (0-10)	NS
Tolerance to cold and heat	5 (0-10)	3.5 (0-10)	6 (0-10)	0.032
Dry skin or hair changes	6 (0-10)	9 (2-10)	4 (0-10)	<0.001
Voice changes	7 (0-10)	9.5 (3-10)	6 (0-10)	<0.001
Motor skills/ coordination	6 (0-10)	8 (1-10)	6 (0-10)	NS
Swelling/ fluid retention	6 (0-10)	9 (1-10)	5 (0-10)	<0.001
Overall physical health	5 (0-10)	6 (1-10)	5 (0-10)	NS
Psychological well being	107 (41-199)	119 (59-199)	103.5 (41-199)	NS
Difficulties coping with disease and treatment	6 (0-10)	7 (2-10)	6 (0-10)	NS
Quality of life	6 (0-10)	6.5 (0-10)	6 (1-10)	NS
Happiness	6.5 (0-10)	7 (1-10)	6 (0-10)	NS
Feel of control of things in life	7 (0-10)	7 (0-10)	7 (0-10)	NS
Satisfaction in life	7 (0-10)	7 (0-10)	7 (0-10)	NS
Ability to concentrate and remember things	5 (0-10)	4 (0-10)	5 (0-10)	NS
Feeling useful	7 (0-10)	7 (0-10)	7 (0-10)	NS
Changes in patient's appearance	5 (0-10)	7 (0-10)	5 (0-10)	NS
Changes in self- concept	6 (0-10)	6 (0-10)	6 (0-10)	NS
Distress caused by: initial diagnosis	2 (0-10)	2 (0-10)	2 (0-10)	NS
surgery	3 (0-10)	3 (0-10)	3 (0-10)	NS
whole treatment	5 (0-10)	5 (0-10)	4.5 (0-10)	NS
initial RI ablation	4 (0-10)	5 (0-10)	4 (0-10)	0.012
whole body scanning	5 (0-10)	6.5 (0-10)	5 (0-10)	NS
thyroglobulin testing	6 (0-10)	8 (0-10)	5 (0-10)	NS
thyroid hormone withdrawal	5 (0-10)	8 (0-10)	5 (0-10)	0.008
Anxiety	5 (0-10)	5 (0-10)	5 (0-10)	NS
Depression	6 (0-10)	7 (0-10)	5 (0-10)	NS
Fear of: future diagnostic tests	5 (0-10)	5.5 (0-10)	5 (0-10)	NS
a second cancer	5 (0-10)	5 (0-10)	7 (0-10)	0.05
recurrence of cancer	5 (0-10)	5 (0-10)	3 (0-10)	0.028
metastases	3 (0-10)	5 (0-10)	2 (0-10)	0.048
Social well being	78.5 (20-129)	82.5 (43-129)	77 (20-125)	NS
Distress in family caused by illness	1 (0-10)	2 (0-10)	1 (0-10)	NS
Support from others	1 (0-10)	1 (0-10)	1 (0-10)	NS
Interferance of illness with relationships	8 (0-10)	8.5 (0-10)	7 (0-10)	NS
Impact on sexuality	8 (0-10)	8 (0-10)	8 (0-10)	NS
Motivation to work	6 (0-10)	7 (0-10)	5 (0-10)	NS
Time away from work	7 (0-10)	8 (0-10)	6 (0-10)	NS
Productivity at work	7 (0-10)	7.5 (0-10)	6 (0-10)	NS
Quality of work	6 (0-10)	6.5 (0-10)	6 (0-10)	NS
Negative impact on: driving a car	9 (0-10)	9 (0-10)	9 (0-10)	NS
household chores	7 (0-10)	9 (0-10)	6 (0-10)	0.004
preparing meals	8 (0-10)	10 (3-10)	7 (0-10)	0.002
leisure activities	7 (0-10)	7 (1-10)	7 (0-10)	NS
Feeling of isolation	10 (0-10)	9.5 (0-10)	10 (0-10)	NS
Financial burden	6 (0-10)	6.5 (0-10)	5.5 (0-10)	NS
Spiritual well being	38 (10-70)	35 (13-60)	39.5 (10-70)	NS
Importance of religious activities	5 (0-10)	5 (0-10)	7 (0-10)	0.043
Importance of spiritual activities	2 (0-10)	1 (0-10)	2 (0-10)	NS
Changes in spiritual life	3 (0-10)	3 (0-10)	3 (0-10)	NS
Uncertainity about future	6 (0-10)	6 (0-10)	5.5 (0-10)	NS
Positive changes in life	5 (0-10)	5 (0-10)	5 (0-10)	NS
Feeling of purpose/mission in life	9 (0-10)	9 (0-10)	9 (0-10)	NS
Feeling hopeful	9 (0-10)	10 (0-10)	9 (0-10)	NS

*P value - NS: not significant

Table 4. Factors associated with physical, psychological, social and spiritual well being score of patients with thyroid carcinoma during levothyroxine withdrawal

Variables	No. of patients	Physical well being		Psychological well being		Social well being		Spiritual well being	
		Coefficient§	P	Coefficient§	P	Coefficient§	P	Coefficient§	P
Age (year)	150	-0.05	0.70	-0.07	0.78	-0.21	0.18	-0.09	0.21
Gender									
Male	36	10.9		13.2		8.1	0.09	–	
Female‡	114	referent	0.010	referent	0.06			–	
Follow-up‡	125	–		–		referent		–	
Radioablation	25	–		–		9.3	0.10	–	
Educational level									
Secondary‡	112	referent		referent		referent		–	
Tertiary	38	6.2	0.15	10.9	0.13	8.3	0.09	–	
TSH (mIU/L)*									
30 to 60‡	33	–		–		–		referent	
61-100	66	–		–		–		-6.15	0.025
>100	51	–		–		–		-3.16	0.016

†Reference category; §Coefficient indicates the change of mean level of physical, psychological, social and spiritual well being score for an increase of 1 year for age, whereas for categorical variables indicates the difference between the mean of score and the respective reference categories. A positive coefficient indicates a better

The average score of psychological well being was 107 (range: 41 to 199) out of maximum 220 points. There were no significant differences by age, sex, education and TSH level. The analysis of patients' individual statements on the PSYWB scale (Table 3) showed that the leading difficulties were distress related to initial diagnosis (2, range: 0 to 10), distress caused by surgical treatment (3, range: 0 to 10), fear of metastases (3, range: 0 to 10) and stress caused by initial radioiodine ablation/treatment (4, range: 0 to 10). Women had significantly lower score than men on distress caused by initial radioiodine ablation/treatment (4, range: 0 to 10 vs 5, range 1 to 10; p=0.012, Mann-Whitney U test) and thyroid hormone withdrawal (5, range: 0 to 10 vs 8, range 1 to 10; p=0.008, Mann-Whitney U test). While men were more fearful of second cancer, women had more fear of recurrence of cancer and metastases.

The median social well being score was 78.5 (range: 20 to 129) out of maximum 140 points. Respondents with higher educational level achieved a significantly higher score than less educated patients (median: 81.5, range 21 to 129 vs. 78, range 20 to 125; p=0.026, Mann-Whitney U test) (Table 2). Illness was very distressing for their families (1, range: 0 to 10) and they reported insufficient support from others (1, range: 0 to 10), but they did not feel isolated (10, range: 0 to 10). Although the examinees did not report great interfering of illness and treatment with their activities at home, women had significantly lower score on statements about negative impact on household chores (6, range: 0 to 10 vs 9, range 0 to 10; p=0.037, Mann-Whitney U test), and preparing meals (7, range: 0 to 10 vs 10, range 3 to 10; p=0.004, Mann-Whitney U test) (Table 3).

In subscale related to spiritual well being the average score was 38 (range: 10 to 70) out of maximum 70 points. Patients reported that they felt very hopeful (9, range: 0 to 10) and sensed a purpose/mission for their life (9, range: 0 to 10). The religious activities were significantly more important for women than men (7, range: 0 to 10 vs 5, range 0 to 10; p=0.043, Mann-Whitney U test) (Table 3).

Male patients had higher physical well being scores than female on multiple regression analysis (Table 4). Although respondents with higher educational level achieved a significantly higher social well being score than less educated patients on bivariate analysis after adjustment for age and other covariates in multivariate analysis there were no significant difference. After adjustment for age patients with higher TSH level had lower spiritual well being score on multiple regression analysis.

DISCUSSION

Successful application of radioiodine as well as thyroglobulin testing requires hypothyroid state which could be achieved either by stimulation of endogenous thyrotropin (TSH) production after withdrawal of levothyroxine therapy or by administration of recombinant TSH (rhTSH). An elevated TSH after thyroid hormone withdrawal leads to hypothyroid state that could be associated with the serious side effects which can have a negative impact on the patient's quality of life (Crevenna et al. 2003, Hassey-Dow et al. 1997). There are many definitions of quality of life (Crevenna et al. 2003, Hassey-Dow et al. 1997, Botella-Carretero et al. 2003). Quality of life (QOL) is defined as an individual perception of position in life, in relation to patient goals, expectations, standards and concerns (Crevenna et al. 2003). Today, in health researches, most commonly used definition is Health related quality of life which is defined by a multidimensional model that consists of

physical, psychological and social well-being. QOL has been extensively evaluated in differentiated thyroid cancer subjects during changes in circulating thyroid hormone levels for diagnostic and therapeutic purposes (Hassey-Dow et al. 1997, Botella-Carretero et al. 2003, Taieb et al. 2011). Therefore, we also tried to find which factors impact mostly on the quality of life of hypothyroid patients and obtained data could be used to improve the educational level of patients, their families as well as medical staff with the possibility of improving life quality through the positive impact of certain aspects of human well being.

In recent reports on QOL in thyroid carcinoma patients many questionnaires were used. Among most commonly used questionnaires are SF-36, SF- 12, Nottingham Health Profile, University of Washington QOL questionnaire, QOL- Thyroid version Questionnaire, City of Hope (Crevenna et al. 2003, Hassey-Dow et al. 1997, Botella-Carretero et al. 2003, Dagan et al. 2004, Kung et al. 2006, Hoftijzer et al. 2008, Brearley et al. 2011). We decided to use QOL- Thyroid version Questionnaire, City of Hope because it is designed specifically for thyroid carcinoma patients, while other questionnaires were made for QOL in general. Patient's compliance with the test was fairly good (response rate 92.5%). The main problems encountered were incompleteness of the questionnaires, and only sometimes refusal to participate in the study because of inconvenience or lack of time, that is comparable with other studies (Lee et al. 2010).

According to different subscales, we expected the lowest results in subscale related to physical well being, which would be compatible to the recent reports on the quality of life after thyroid hormone withdrawal where a significant reduction in physical and psychological quality of life was observed (Hassey-Dow et al. 1997). The analysis of patient's individual statements on the physical (PHWB) subscale showed that our patients had most difficulties with fatigue, intolerance to cold and heat, sleep changes, and weight gain, but with higher average values than expected. As in other reports, fatigue was one of three most common physical difficulties (Davids et al. 2006). Female patients had significantly more difficulties than male respondents with following symptoms: fatigue, appetite changes, sleep changes, dry skin or hair changes, voice changes and swelling/ fluid retention but less with tolerance to cold and heat.

The individual statements based on the phychological (PSYWB) scale showed that the leading difficulties were distress related to initial diagnosis, distress caused by surgical treatment, fear of metastases and stress caused by radioiodine ablation. Women had significantly lower score than men on distress caused by initial radioiodine ablation/treatment and thyroid hormone withdrawal. Generally, women had more fear of recurrence of cancer and metastases. The leading difficulties in each group of questions remained mostly the same in other studies (Davids et al. 2006).

According to social well being, in our study, respondents with higher educational level achieved a significantly higher score than less educated patients. One another study has shown that there was a significant decrease in quality of life in poorer educated patients and in elderly (Tan et al. 2007). Furthermore, other studies have shown that variables such as education, religiosity and elapsed time interval since initial diagnosis were not correlated with depression and anxiety (Tagay et al. 2007). Other work has shown that education and occupation modified the effect of cancer on the employment; the difference between cancer survivors in the probability of being employed was greater in the lower than in the higher educational groups (Taskila-Abrandt et al. 2004).

Generally, the examinees did not report severe interfering of illness and treatment with their activities at home. As expected, women had significantly lower scores on statements about negative impact on household chores and preparing meals which is understandable since women still do most of the housework in our community.

In subscale related to spiritual well being patients reported that they felt very hopeful and sensed a purpose/mission for their life. The religious activities were significantly more important for women than men, but all of them changes spiritual activities allowed them higher importance after establishing a diagnosis of malignant disease.

Male patients had higher physical well being scores than female on multiple regression analysis in our investigation. Although respondents with higher educational level achieved a significantly higher social well being score than less educated patients on bivariate analysis after adjustment for age and other covariates in multivariate analysis there were no significant difference. After adjustment for age patients with higher TSH level had lower spiritual well being score on multiple regression analysis. Since there are findings in the literature that describe better quality of life in patients younger than 45, male patients and patients with higher level of education (Dagan et al. 2004, Tan et al. 2007, Tagay et al. 2007, Taskila-Abrandt et al. 2004), we expected similar findings in our study, but after dividing our patients into groups according to age, gender, current employment status, TSH level and reason for hospitalization we noted only difference in particular difficulties, mostly in gender groups. Similar findings were noted in another study (Dagan et al. 2004).

Most respondents indicated that their quality of life was quite good, in general. Illness was very distressing for their families but they did not feel isolated. Respondents also indicated a desire for adequate information about the disease, signs of recurrence, and recent developments in thyroid cancer treatment. Recent reports have also emphasized the need for more patient information and support (Roberts et al. 2008). Having that in mind, we should provide to patients access to

proper and complete information about their disease and, if possible, contacts of support groups.

In many reports most common difficulty is fatigue which reminds us that despite positive influence of psychological, spiritual and social well being, physical difficulties are still present and can cause QOL impairment in certain patients and disable normal daily functioning (Davids et al. 2006). In that case, some symptoms, mostly physical, could be diminished by using recombinant TSH and avoiding hypothyroidism (Schroeder et al. 2006). Recombinant human TSH is a source of exogenous TSH and its administration to thyroid cancer patients remaining on thyroid hormone therapy promotes radioiodine uptake by thyroid cells with the same efficacy as hypothyroidism but with preserving the patient's quality of life. More recently, the clinical benefits of the use of rhTSH versus thyroid hormone withdrawal on the preservation of QOL have been demonstrated (Lee et al. 2010, Schroeder et al. 2006). Because of the relatively high price of rhTSH its use is limited and sometimes not under reimbursement policy of health insurance. The second way to avoid these difficulties is possible reducing the period of hypothyroidism. The total TSH concentration in the serum of our patients were above the upper limit of normal values, which means higher than 30 mIU/L (normal range 0.40-4.2 mIU/L) that seems desirable for nuclear-medicine procedures in thyroid cancer patients. Moreover, the average value of TSH at the time of measurement in our patients after four weeks withdrawal were significantly higher, so in order to reduce the period of hypothyroidism with all unintended consequences this period could be shortened. According to the literature, the minimum required concentration of TSH absolute level of 30 mIU seems arbitrarily determined, and there are no data to describe the quality of scintigraphic display as well thyroglobulin testing and success of ablation as a function of the different concentration of TSH in serum (Medvedec 2006). Here, it seems also important to consider patient's age because it is observed that there is a rapid increase of TSH at a younger age, than in older patients, although this was not the subject of this research. For exploring reason, patients divided into three groups according to TSH level, and showed compatible results (Table 4). Likewise, we found no relationship between different values of TSH level between three groups of patient (>30-60, 60-100, and>100). Since the patients (at the time of four week withdrawal) multiple exceeded the recommended value (>30 mIU/L), it could be concluded that the target TSH value can be achieved in a shorter time than twice normal. Therefore, the value of TSH could be measured two weeks after omission of hormone replacement therapy and if the target value is reached immediately performed diagnostic and therapeutic procedures which would guarantee a significantly shorter average duration of hypothyroid condition of the patient. The modes of treatment (ablation or control) and different level of TSH did not affect a grade of symptoms in this study. As in another study (Tagay et al. 2007) the TSH level as an indicator of hypothyreodism did not correlate with depression or with anxiety on a significant statistical level.

Despite these interesting findings, our study suffers from several possible limitations. First, it is limited by lack of comparison with a healthy control group and a lack of information regarding specific details about thyroid cancer stage as well as type of treatment. Further investigation with a larger number of ablation patients with more demographic and pathohystologic data is needed. Furthermore, the including of the healthy control group with normal values of TSH (euthyroid patients) with data comparison should be performed. The study was designed as a cross-sectional survey and as such did not allow any causative conclusions. Another limitation of the study could be the length of the questionnaire. It is possible that patients became tired after a number of questions and did not concentrate on the answer by the end of the test. Also, spiritual well being subscale had week internal consistency, hence the results of this score should be interpreted with caution. With these limitations in mind, we believe that our study provides evidence of high-risk areas in patients lives that are negatively affected by hormone withdrawal.

CONCLUSION

The impact of thyroid hormone withdrawal on QOL showed significant changes in physical, psychological, and social well-being across the four testing points. While it is generally known that patients have physical symptoms relating to thyroid hormone withdrawal, the greatest changes occurred in psychological (distress caused by initial diagnosis, surgery, ablation, fear of metastases), and social (distress in the family caused by illness) spheres that emerged as the strongest determinants for most of the domains in the questionnaire that could have a negative influence on global health. Improvement in quality of life in DTC patients can be achieved by directing our attention to specific areas of physical, social and psychological well being. Patients need to be encouraged to talk about their dilemmas and problems through active conversation with physicians who should provide a detailed explanation of the nature of their disease, possible difficulties and course of recovery. Physicians could help to improve QOL and reduce the increased anxiety among patients by informing and teaching them how to manage these uncomfortable symptoms with the possibility of development of educational groups. Since short-term hypothyroidism accounts for a substantial proportion of the QOL impairment, this situation could be improved by avoiding hypothyroidism and applying rhTSH instead. Data which has been obtained could be used to achieve a positive impact and better recovery of patients by directing our attention to most expressed difficulties noted in this questionnaire.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 528-532 *Original paper*

DRY EYE IN CONTACT LENS WEARERS AS A GROWING PUBLIC HEALTH PROBLEM

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SUMMARY

Background: *The aim of this study is to analyze the relationship between the self-reported symptoms and objective signs of dry eye disease in long-term rigid gas-permeable (RGP) or soft contact lens (SCL) wearers.*

Subjects and methods: *The study included 84 eyes of Caucasian RGP and SCL wearers between the age of 15 and 71 who wore contact lenses on a continuous daily basis for more than 1 year. Symptoms were assessed according to the Ocular Surface Disease Index (OSDI). Clinical assessments included corneal fluorescein staining according to the National Eye Institute (NEI) staining grid and tear film break-up time (TBUT).*

Results: *There were more female (76.19%) than male (23.81%) persons with a higher proportion of RGP wearers among the females (88.89% vs. 11.11%). The mean duration of daily lens wear was 7.71±2.72 hours. No RGP wearer in this study had a NEI corneal staining grid score higher than 2. A weak negative correlation was found between daily lens wear duration and TBUT (Pearson's coefficient, r=-0.1467). A strong negative correlation was found between TBUT and OSDI values (r=-0.844).*

Conclusion: *The results of the study emphasize the importance of early and accurate diagnosis of dry eye disease for successful long term RGP and SCL contact lens wear. This will hopefully motivate future larger scale investigations on dry eye related problems in contact lens wearers.*

Key words: *dry eye - soft contact lens - rigid gas-permeable contact lens - Ocular Surface Disease Index (OSDI) - tear film break-up time (TBUT)*

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INTRODUCTION

Dry eye syndrome is recognized as a growing public health problem and one of the most frequent reasons for seeking ophthalmological intervention (Kaštelan et al.2013a, Kaštelan et al 2013b, Behrens at al 2006). Dry eyes, redness and foreign body sensation are common complaints among contacts lens wearers (Kaštelan et al. 2013a) with these symptoms being more prevalent in contact lens wearers than in the general population (Nichols et al. 2005). Due to changes associated with dry eye these persons also often complain of visual impairment and blurred vision (Tutt et al. 2000). The mentioned symptoms and disturbances appear to be more common in the evening than during the day (Begley et al. 2000).

Previously conducted investigations estimate that the frequency of contact lens related dry eye is approximately 50% (Nichols et al. 2005, Tutt et al. 2000, Guillon et al. 1997). Besides blurred vision dry eye symptoms in contact lens wearers is also associated with reductions in daily wearing time and an increased risk of ocular surface dryness and infection (Young et al. 2004, Ladage et al. 2001). Discomfort and desiccation symptoms are the primary reasons for contact lens intolerance, a reduction in the length of wearing time and eventual discontinuation (Richdale et al. 2001). In a study conducted to investigate the reasons for cessation of wearing contact lenses 51% of the participants reported discomfort as the main reason (Young et al. 2002). It has been suggested that potential pathogenesis of contact lens-related dry eye include tear hyperevaporation, inflammation of the ocular surface, reduced capability of tear glands to produce tears of optimal composition with concurrent increased osmolarity, hormonal changes and disturbances, dryness related to lack of biocompatibility of the lens surface or any combination of these mechanisms (Kaštelan et al. 2013a, McMahon et al. 2000, Lemp et al. 1995, Gilbard et al. 1986, Gotovac et al. 2013, Nichols & Sinnott 2006). The diagnosis of dry eye is set on the basis of self-reporting of symptoms and clinical examinations (Kaštelan et al. 2013a). The examinations usually include the tear break up time test (TBUT) as an indicator of tear film stability, the Schirmer test which measures the tear production as well as corneal and conjunctival staining for assessment of ocular surface epithelial damage (O'Brien & Collum 2004). However, the correlation between the dry eye subjective symptoms severity and clinical dry eye tests are frequently inconsistent (Lemp et al. 1995, O'Brien & Collum 2004). To facilitate the diagnosis several patient-reported outcome (PRO) questionnaires are available so as to give useful information which can aid in the identification and assessment of the severity of dry eye disease symptoms (Kaštelan et al. 2013a). The Ocular Surface Disease Index (OSDI) is one of the most commonly used PRO questionnaires and includes the three segments namely ocular symptoms, vision-related function and environmental triggers (Walt 2004).

It is known that long-term contact lens wear may decrease corneal thickness and increase the corneal curvature with surface irregularity (Pflugfelder et al. 2002). However, despite a significant change in materials and designs of RGP lenses in the last 20 years and a significant number of RGP fits in some Western countries, there is still a lack of evidence regarding differences in dry eye symptoms and signs between long term RGP and soft contact lenses wearers (Efron et al. 2012).

The aim of this report is to analyze the relationship between the subjective self-reported symptoms and objective signs of dry eye disease in patients who wear rigid gas-permeable (RGP) or soft contact lenses (SCL) (Kaštelan et al. 2013a).

SUBJECTS AND METHODS

Subjects

The study included 42 Caucasian (84 eyes) daily long-term wearers of rigid gas-permeable and soft contact lens between the ages of 15 and 71 with the prerequisite being that they wear contact lenses on daily basis continuously for more than 1 year. Patients being treated for ocular infection within 4 weeks, those who used artificial tear preparations within one week, had a history of refractive and other corneal surgeries or presented with eyelid anomalies were excluded from the study. The lens materials varied in their oxygen permeability (Dk) values. The Dk value of RGP lenses worn by participants was between 28 and 100 Dk whereas the soft lens materials had Dk values between 9 and 110.

Methods

Symptoms of ocular dryness were assessed using the Ocular Surface Disease Index (OSDI). The OSDI scores were calculated according to the formula recommended by Schiffman et al. (Schiffman et al. 2000). The Ocular Surface Disease Index (OSDI), developed by the Outcomes Research Group at Allergan Inc., is a reliable 12-question survey designed to measure the severity of dry eye symptoms and evaluate how they affect vision-related functioning. This instrument elicits responses on three subscales: vision-related function (watching TV, reading), ocular symptoms (grittiness, blurred vision) and environmental triggers (low humidity, high wind). In addition to effectively discriminating among normal, mild to moderate and severe dry eye disease with good to excellent reliability. OSDI results are quantitative and suitable for statistical analysis. The Ocular Surface Disease Index (OSDI) rates dry eye severity on a scale of 0 to 100. For each question, patients choose a number between 0 and 4 to describe their symptoms, where 0 indicates none of the time, 1 some of the time, 2 half of the time, 3 most of the time and 4 all the time. If a patient chooses 2 for all the questions, his OSDI score would be 50. The lower a patient's score, the fewer dry eye symptoms and vice versa.

The additional questionnaire included data on average daily contact lens wear time and systemic and/or local therapy. Clinical assessments included corneal fluorescein staining and tear film break-up time (TBUT).

Corneal staining was graded using the National Eye Institute (NEI) staining grid in which a score of 0-3 (0 - normal and 3 - severe) was assigned to each of five corneal regions (central, nasal, temporal, superior and inferior) with a maximum total score of 15. Patients were divided in two groups depending on the corneal staining score for each eye with a grade <2 in either zone representing the threshold for a normal finding.

Statistical analysis

Statistical data analysis was based on inferential statistics performed with commercially available software (SPSS ver. 10.0 for Windows). Our goal was to estimate the difference in population proportions and determine the correlation between tested variables by using the Pearson's correlation coefficient (r). As the tested variables had no functional relationship, correlation analysis was used to determine the strength of the statistical or stochastic relationships.

RESULTS

Table 1 presents the structures of the participants according to gender, age, daily lens wear. The results are shown for the entire group and in relation to three levels of OSDI (Ocular Surface Disease Index) values. There were more females (76.19%) than male (23.81%) patients, with 83.33% of them having moderate OSDI score. A mild OSDI score had 71.43% female participants, which is less than expected regarding the proportion of females in the whole sample (76.19%). There were fewer males than expected regarding the sample with a moderate OSDI score (16.67%). More males compared to the total share (23.81%) of males in the sample have a mild score (28.57%). The mean age of all contact lens wearers was 36.86±16.31 years with a range from 15 to 71 years of age and median value being 36.5 years. The patients wore their lenses from 1 to 31 years prior to presentation (11.64±7.88 years). Daily lens wear duration was from 4 to 13 hours with an average of 7.71±2.72. From the total number of respondents 50% wore daily lenses less than or equal to eight hours and the remaining 50% of the respondents wore them for 8 hours and longer. The age structure shows that the largest proportion of the participants were younger than 30 years of age namely 47.62%. It was noted that normal OSDI score related to age had a similar structure. In the moderate OSDI score level the participants at the age up to 30 have a smaller proportion (33.33%) than expected according to the results at the sample level (47.62%). The age group from 30 to 50 years of age accounts for a significantly larger part (50%) for the moderate OSDI scores level compared to the share of this age group in the actual sample (30.95%).

Table 1. The relative frequency of normal, mild and moderate OSDI scores according to gender, age, duration of daily lens wear and TBUT

		Total N (%)	OSDI Normal N (%)	OSDI Mild N (%)	OSDI Moderate N (%)
Gender	Male	20 (23.81)	6 (20.00)	12 (28.57)	2 (16.67)
	Female	64 (76.19)	24 (80.00)	30 (71.43)	10 (83.33)
	Total	84 (100)	30 (100)	42 (100)	12 (100)
Age (years)	15-30	40 (47.62)	14 (46.67)	22 (52.38)	4 (33.33)
	30-50	26 (30.95)	10 (33.33)	10 (23.81)	6 (50.00)
	50-70	18 (21.43)	6 (20.00)	10 (23.81)	2 (16.67)
	Total	84 (100)	30 (100)	44 (100)	12 (100)
Daily lens wear Duration (hours)	≤8	48 (57.14)	18 (60.00)	24 (57.14)	6 (50.00)
	>8	36 (42.86)	12 (40.00)	18 (42.86)	6 (50.00)
	Total	84 (100)	30 (100)	42 (100)	12 (100)
TBUT*	Pathological	38 (45.24)	6 (20.00)	20 (47.62)	12 (100.00)
	Normal	46 (54.76)	24 (80.00)	22 (52.38)	0 (0)
	Total	84 (100)	30 (100)	42 (100)	100 (100)

*p<0.01 (Chi-squared test of independence confirmed the dependence of variables TBUT and OSDI with 1% significance); OSDI - Ocular Surface Disease Index; TBUT - Tear Break-up Time

Table 2. The relative frequency of soft and rigid gas-permeable wearers according to gender, age, duration of daily lens wear, TBUT and OSDI

		Lens type SCL N (%)	Lens type RGP N (%)	Total N (%)
Gender	Male	18 (27.27)	2 (11.11)	20 (23.81)
	Female	48 (72.73)	16 (88.89)	64 (76.19)
	Total	66 (100)	18 (100)	84 (100)
Age (years)	15-30	34 (54.55)	4 (22.22)	38 (47.62)
	30-50	20 (27.27)	8 (44.44)	28 (30.95)
	50-70	12 (18.18)	6 (33.33)	18 (21.43)
	Total	66 (100)	18 (100)	84 (100)
Daily lens wear Duration (hours)	≤8	44 (66.67)	4 (22.22)	48 (57.14)
	>8	22 (33.33)	14 (77.78)	36 (42.86)
	Total	66 (100)	18 (100)	84 (100)
TBUT	Pathological	28 (42.42)	10 (55.56)	38 (45.24)
	Normal	38 (57.58)	8 (44.44)	46 (54.76)
	Total	66 (100)	18 (100)	84 (100)
OSDI	Normal	22 (33.33)	8 (44.44)	30 (35.71)
	Mild	36 (54.55)	6 (33.33)	42 (50.00)
	Moderate	8 (12.12)	4 (22.22)	12 (14.29)
	Total	66 (100)	18 (100)	84 (100)

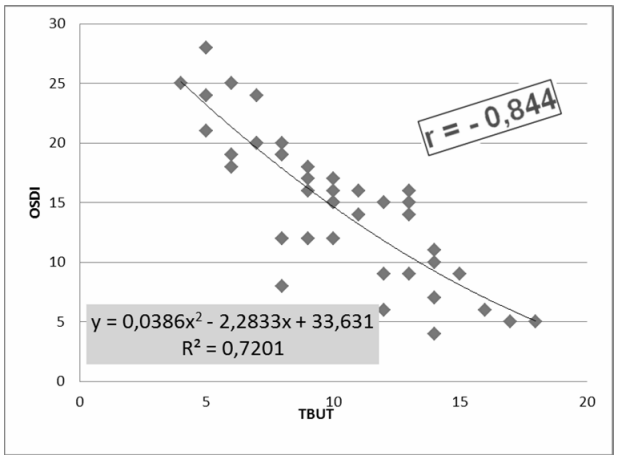
TBUT - Tear Break-up Time; OSDI - Ocular Surface Disease Index; SCL - Soft Contact Lens; RGP - Rigid Gas-Permeable

The structure of the participants was analyzed according to gender, age, hours of daily lens wear and the TBUT value, separately for SCLs and RGPs wearers (Table 2). Regarding age, the ratio between males and females was 27.27% as opposed to 72.73% for SCL wearers and 11.11% of males and 88.89% females in RGP contact lens wearers. The participants included in the study according to their age were divided into classes up to 30 years, between 30 and 50 and from 50 to 70 years of age and older. The majority of the respondents wearing SCLs were younger than 30, whereas those wearing RGPs accounted for 22.22% which is significantly less than the share in the sample (47.62%). The participants older than 30 years of age to a larger extent opted for RGPs. The mean duration of daily lens wear was 7.71±2.72 hours, with a significantly higher proportion of patients who wore their lenses for prolonged hours in the soft contact lens group ($p<0.05$). No RGP wearer in this study had a NEI corneal staining grid score higher than 2.

The number of daily hours of wearing contact lenses in the whole sample size has been distributed as follows: 57.14% wearing lenses less or equal to 8 hours. Further, regarding SCLs wearers there are as many as

66.67% who wear them for less or equal to eight hours daily. Alternatively in the group of RGPs users there are only 22.22% who wear lenses less or equal to eight hours daily with the majority wearing them for more than eight hours daily. The TBUT values have been divided into two groups: the pathological and the normal. In SCL wearers 42.42% have a pathological level of TBUT. For the RGP users the situation is more favorable with 30% of them having a pathological TBUT level. In the whole sample there were 45.24% of participants with pathological TBUT levels.

Figure 1 presents a scatter diagram of the correlation and regression of TBUT and OSDI showing a statistically significant negative correlation of TBUT and OSDI scores with Pearson's correlation coefficient r=-0.844.



p<0.01, OSDI - Ocular Surface Disease Index, TBUT - Tear Break-up Time

Figure 1. Scatter diagram of the correlation and regression of TBUT and OSDI

DISCUSSION

Dry eye is a multifactorial disease of the tears and ocular surface with symptoms that often fail to correspond to diagnostic testing (Kaštelan et al. 2013b). It is a widespread problem that may often be overlooked since it is not a common cause of permanent visual morbidity (Schaumberg et al. 2002, Latkany 2008). However, newer concepts suggest that dry eye syndrome can have a significant impact on visual function diminishing the everyday quality of live (Goto et al. 2002). Left untreated, the wearer may experience not only discomfort and visual disturbances but also ocular inflammation and scarring of the corneal surface and permanent damage (Latkany 2008, Goto et al. 2002). Management of ocular surface disorders requires thorough history and ophthalmological examination. The incorporation of a questionnaire may facilitate the evaluation of patients and aid in setting a diagnosis. A variety of treatment modalities are currently available and the selection of treatment can be simplified by classifying symptoms on a continuum from mild to severe and thereby choosing therapies that target the underlying inflammatory process with the goal of restoring the normal tear film and function (Kaštelan et al. 2013b). To overcome these issues, practitioners need to know how to evaluate dry eye symptoms and offer the best lens materials and care solutions in order to relieve patient's discomfort. This study suggests that OSDI scores may be useful for assessing dry-eye related discomfort in contact lens wearers. When used as an adjunct to objective TBUT testing, subjective OSDI scores may help practitioners evaluate the severity and identify possible causes of dry eye symptoms and at the same time testing regimen can help evaluate ocular changes associated with contact lens materials and care solutions.

Contact lens wear compromises the precorneal film stability and causes the disappearance of the lipid layer in the post-lens fraction which is responsible for the tear film stability. Furthermore this separation of tear film triggers an increase of water evaporation (Doughty 1999) followed by a corresponding increase of the tear osmolarity and consequently resulting in ocular surface damage (Gilbard et al. 1986, Stahl et al. 2012, Foulks 2007). During long time wearing of contacts these changes may become more pronounced and the effect of contact lens precorneal position is accumulated over time which manifests as a stronger feeling of discomfort consequently meaning a higher OSDI score (Kaštelan et al. 2013b). It is hypothesized that mechanisms other than tear film separation, such as changes in corneal epithelium and/or cytokine production, may also contribute to the poorer TBUT and OSDI values in long term wearers. Furthermore we should be aware that there is an increasing number of contact lens wearers being treated due to glaucoma with additional negative influence on tear film stability (Salopek-Rabatić et al 2013, Tomić et al. 2013, Kaštelan et al. 2013c).

Our investigation was conducted as a pilot study with a smaller number of participants. Nevertheless, motivating results were obtained particularly considering the small number of publications addressing the differences in symptoms and signs of dry eye in RGP and soft lens wearers in the last few decades. We hope that this study will encourage researchers to conduct larger scale investigations on dry eye related problems in RGP and soft lens wearers in the future. The presented correlations, although in most cases weak or moderate, show trends that may assist in advising, monitoring and ultimately treating contact lens wearers.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 533-536 *Original paper*

THE PROFILE OF SCABIES PATIENTS IN ZAGREB

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SUMMARY

Background: *Scabies is a mandatory notifiable disease according to Croatian law. Due to an increased reports of scabies within a couple of years in Zagreb, we decided to present epidemiological characteristics of patients diagnosed with scabies in Zagreb.*

Subjects and methods: *A retrospective survey was carried out in county Public Health Institute "Dr. Andrija Stampar" in Zagreb and analysis was performed for the period of 2010-2013 upon individual notifications on scabies cases. The patients are presented by sociodemographic data, diagnosis and treatment.*

Results: *In a 4 year period there were 246 scabies cases recorded in Zagreb. Cases have been registered in all quarters of the City. The highest incidence (50/100 000) was recorded in every child age group following by incidence of over 30/100 000 in elderly institutionalized in nursing homes. In almost two thirds of patients management of scabies has not been conducted in accordance to current guidelines. 10% of scabies cases were found in medical health personnel predominantly in those working in nursing homes and psychiatric wards. A small amount of cases 19 (8%) were infected outside Croatia; the majority of these cases 15 (78%) are registered within last two years.*

Conclusion: *High percentage of scabies cases registered in nursing homes and psychiatric wards suggests that there is a need of raising awareness on scabies epidemiology and management by public health officers. Due to a higher incidence of scabies in children age, the obligation of medical practitioners is also to emphasize the importance of following treatment guidelines. In order to control scabies cases as well to prevent outbreaks within hospital wards or nursing homes there is an obligation of implementation of strict guidelines regarding treatment of scabies and a public health service referral*

Key words: *scabies – epidemiology – Zagreb - nursing homes - psychiatric wards*

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INTRODUCTION

Scabies is parasitic skin infection, caused by infestation with a mite Sarcoptes scabiei var. hominis. It is estimated that 300 million cases of scabies occur globally every year, but the disease is not notifiable in many countries so data could vary (WHO 2014, CNIPH 2014, CDC 2014). Scabies has a worldwide distribution, the disease is endemic and highly prevalent within the countries of the developing world in resource poor settings (Heukelbach et al. 2006, Heukelbach et al. 2013). Scabies is one of the 17 neglected tropical diseases prioritized by WHO due to a fact that scabies contribute to overall morbidity substantially; in 2010 it was estimated that the direct effects of scabies infestation on the skin alone led to more than 1.5 million YLDS (years lived with disability) (Johns et al. 2013, WHO 2014).

In high income countries scabies outbreaks have been reported in long – term care facilities and hospitals, often originated after a single undiagnosed or incompletely treated case (Heukelbach et. al 2006, Makigami et al. 2009, Amor et al. 2012).

All human are susceptible to the acquisition of scabies, but transmission is more often in nursing homes, psychiatric wards, asylum centres; but also in children and immunosuppressed persons. Prevalence within the child population in resource poor countries is 5-10% (Muhammad Zayyid 2010, Heukelbach 2013). Scabies can be complicated with secondary bacterial infection (Streptococcus pyogenes and Staphylococcus) and lead to systemic infection which increases morbidity and hospitalization rate, as well as the financial costs of treatment (Hay et al. 2012).

Beside typical clinical signs, the definitive method for scabies diagnosis is skin scraping with identification of mites and eggs (Hengge et al. 2006, Chosidow 2006). Also dermoscopy can be used, particularly in patients where some difficulties to obtain skin scraping (children, immunocompromised) (Towersey et al. 2013).

Scabies is treated with locally applied scabicides (permethrin, lindane, benzyl benzoate, crotamiton); the choice is made upon: availability of drugs, age of patients, and life condition of patients (Hengge et al. 2006, Mounsey et al. 2013). Excellent results provide orally used ivermectin especially when it's used in institutional outbreaks, but it is not licensed in many countries, and it is contraindicated in children below 15kgs and pregnant or lactating women (Fawcett 2003).

In Croatia, scabies is notifiable disease since 1971 (CNIPH 2014). In the last decade, approximately 600 cases per year is recorded, respectively 60 cases in Zagreb (CNIPH 2014).

During the past several years in Zagreb we noticed an upsurge of scabies notifications, not only in nursing homes and psychiatric wards but also an increase of sporadic cases or minor family outbreaks. We analysed a period from 2010-2013 in order to have a better insight of epidemiological characteristics of our cases. Our aim is also to adapt a wide range of existing scabies management procedures and to tailor it to the current needs.

SUBJECTS AND METHODS

A retrospective survey was carried out in county Public Health Institute "Dr. Andrija Stampar"in Zagreb, Department of epidemiology for infectious disease. The data were obtained from individual notifications on infectious diseases, which is mandatory under Croatian law. (Official Gazette 2007) Data were collected for the years 2010-2013 inclusive and were examined by week and then aggregated to provide annual incidence rate in age specific groups. (0-4, 5-9, 10-14, 15-19, 20-29, 30-39, 40-49, 50-59, >60). Rates are presented per 100 000 age-specific person-years.

This study was conducted using a questionnaire developed for this research that contained demographic data, patient history, diagnostic methods, prescribed treatment and duration of treatment and finally the number of contacts put on treatment due to an index patient.

An investigation and consultation is carried out by a medical doctor specialized in epidemiology in patient's homes, hospital and nursing wards, according to notifications.

RESULTS

From 2010 to 2013 included, 246 cases of scabies have been recorded, which accounts 10% of all scabies notifications in Croatia within the same period. The crude incidence rate of 21.2/100 000 was found in Croatia in 2013. In the last two years incidence rate has doubled in Zagreb from 5/100 000 in 2010 and 2011 to 9.7 /100 00 in 2012 and 11.6/100 000 in 2013. Scabies is registered in all quarters of Zagreb, the highest incidence rate within the last two years has been recorded in Sesvete (44.3/100 000 in 2012; 2013.-22.9/100 000 in 2013); following by Pescenica and Maksimir. A high incidence rate of 44.3/100 000 is a result of epidemic in a nursing home. Overall, almost equal number of men and women were reported. (M 52%; F 48%). The incidence rate of over 50/100 000 was found in child age (0-5, 5-9, 10-14, 15-19 years). A substantial proportion of cases (38%) was found in elderly (60 years and older) with an incidence of 33.2/100 000.

Only 17% of registered cases live in poor living conditions. One third of cases (working age population) are unemployed. Over the half of recorded cases was diagnosed by dermatologists. A diagnosis made by skin scraping has been performed in two thirds of cases, with an extremely high proportion (94%) of positive results (mites, eggs and scybala were found). In 37% of cases, the treatment has been conducted during 5 days (with benzyl-benzoate), almost 1/5 of scabies cases has undergone treatment for a more than a month. 65% of cases live within families, 19% are institutionalized. In a quarter of registered cases scabies did not affect their families, sexual partners, other residents of nursing homes or other patients admitted on the same hospital ward. 10% of scabies cases were found in medical health personnel predominantly in those working in nursing homes and psychiatric wards. A small amount of cases 19 (8%) were infected outside Croatia; the majority of these cases 15 (78%) are registered within last two years. Half of the cases infected abroad have been infected in our neighbouring countries (Bosnia and Hercegovina, Serbia). Immigrants comprise only 10% of scabies reports within an observed period.

DISCUSSION

Infectious diseases reporting system is mandatory and regulated by law, and for scabies is conducted from 1971 (Official Gazette 2007, CNIPH 2014). Even though scabies does not contribute significantly to all notifications on infectious diseases, during the last year in Croatia and within two years in Zagreb a number of notifications has doubled. The analysis of cases in Zagreb as well as in other economically developed countries shows that scabies cases are not related with bad hygiene and poverty but are mainly a result of late diagnosis and misdiagnosis (Laya et al. 2011, Hewitt et al. 2014). Similarly as in Belgium and UK, the highest incidence rate (50/100 000) was found in child age (0-4, 5-9, 10-14, 15-19 years) (Lapeere et al. 2008, Lassa et al. 2011). In our study all of these children live in families which indicate a lack of awareness of urgent and immediate scabicide treatment needed if there is a scabies case in the family. Little less than a half of patients were diagnosed by primary care physicians, and majority of them where diagnosed clinically so there is a possibility that the real number of scabies cases may be underestimated, especially in those with milder clinical symptoms or some other concordant dermatological disorder. (Jeanneret et al. 2007)

In almost two thirds of patients management of scabies has not been conducted in accordance with current guidelines which suggests to incompletely applied therapy and the possibility of re-infection, mainly in nursing homes and among people with lower socioeconomic status as seen also in other countries (Scheinfeld 2004, Badiaga et al. 2008, van de Hoek et al. 2008).

In 75% of cases, infestation with scabies has been transmitted to close contacts (family, sexual partners, residents of nursing homes) which are more often recognized in resource poor settings, which implies that either medical practitioners are not familiar with guidelines regarding treatment nor do household contacts don't comply with therapy (Chouela et al. 2002, Hicks et al. 2009, Scott et al. 2011).

A substantial percent of scabies cases is recorded among health care personnel (HCP) which is noticed also among other health care institutions in Europe and USA. In these countries scabies cases are not as prevalent as in endemic countries, so HCP are not familiar with epidemiological characteristics of scabies and also rarely see atypical clinical presentations of cases (Larrosa et al. 2003, Scheinfeld 2004, Vorou et al. 2007, Buehlmann et al. 2009).

8% of our scabies cases have been infected with scabies outside Croatia, but there is an upsurge of these cases within last 2 years. This reflects the situation in our close neighbourhood where the prevalence of scabies is 35.6/100 000 in 2011 (ZZJZBiH 2011, ZZJZBiH 2013). Minority of scabies patients are within immigrant population that is somewhat different from other studies of scabies that are mainly driven by immigrant population (Lapeere et al. 2008, Pérez-Crespo et al. 2014)

There are several possible limitations of the study. The survey was performed only on official notifications of scabies cases, so it could be that scabies is under-reported as well as any other infectious disease in Croatia due to a lack of computerized system of registration of communicable diseases. We also do not know what is the proportion of scabies cases among all other dermatoses as well as what is the rate of systemic complications due to a scabies infection. The data were not linked with pharmacies so it is not known how many drugs for treatment of scabies was sold over the counter (OTC).

CONCLUSION

Even though our surveillance of infectious diseases is passive, it gives us a good insight of trends. It also indicates the need of epidemiological investigation of scabies cases in order to have a better understanding of characteristics of patients.

There is a need of raising awareness on scabies in health care personnel as well as in general public with the information about disease and the management of disease. In order to control scabies cases as well to prevent outbreaks within the hospital wards or nursing homes, there is an obligation of implementation of strict guidelines regarding treatment of scabies. Nevertheless, there is also a demand to monitor and supervise all scabies cases and contacts in case of outbreaks, plus early involvement of responsible public health service. All above measures point out that a public health officials should be involved promptly in the management of scabies in order to enhance surveillance and to monitor the conduction of guidelines.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 537-545 *Original paper*

FOOD SAFETY IS AN IMPORTANT PUBLIC HEALTH ISSUE: CHLORAMPHENICOL RESIDUES DETERMINATION BY LIQUID CHROMATOGRAPHY TANDEM MASS SPECTROMETRY (LC-MS/MS) IN HONEY

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SUMMARY

Background: *Honey is used for nutritional, medicinal and industrial purposes and antibiotic residues may harm its quality and constitute a danger to human health. The broad spectrum antibiotic chloramphenicol (CAP) was used for curative purposes in veterinary medicine, but is now forbidden in European Union (EU) because of its many serious side effects (e.g. aplastic anaemia, grey syndrome, severe bone marrow depression and hypersensitivity).*

The aim of this study was to facilitate analyses of the quality and safety of Croatian honey distributed to whole European Union market; an assessment that has not previously been made.

Subjects and methods: *CAP in honey was qualifying and quantifying by validated liquid chromatography tandem mass spectrometry with negative electrospray ionisation method (LC-MS/MS). The target antibiotic was separated on chromatographic column Zorbax SB C18 (150 mm × 2.1 mm, 3.5 μm) with a gradient elution using acetonitrile - 0.1% formic acid mobile phase at a flow rate of 0.3 mL/min, with column temperature 35 oC for CAP and 5D-CAP as internal standard. Homogenised honey samples were diluted with acetate buffer solution and extracted on Oasis Hydrophilic-Lipophilic-Balanced (HLB) sorbents. The method was used to analyse 280 domestic honey samples collected throughout Croatia between 2005.–2013.*

Results: *Recoveries of the method for real (acacia, chestnut, linden and flower) honey samples were 102% with RSD 8.4%. The value CCα and CCβ were 0.09 and 0.12 μg/kg, respectively. Results showed only three subsequent positive detections (1.1%) of CAP in honey.*

Conlusions: *Analysed honey samples from Croatia showed good quality and safety what is the one of the main objective in consumer health policy in EU.*

Key words: *antibiotics – chloramphenicol - honey - liquid chromatography tandem mass spectrometry (LC-MS/MS)*

* * * * *

INTRODUCTION

Honey, defined by European Commission, is the natural sweet substance produced by Apis mellifera bees from the nectar of plants or from secretions of living parts of plants or excretions of plant-sucking insects on the living parts of plants, which the bees collect, transform by combining with specific substances of their own, deposit, dehydrate, store and leave in honeycombs to ripen and mature (Council Directive 2001/110/EC). In the long human tradition it has been used not only as nutrition but also as a medicine. The belief that honey is nutrition, a drug and an ointment has continued to the present time. Currently, information on the use of honey for the treatment of many human diseases can be found in general magazines, beekeeping journals and natural products leaflets, suggesting a wide variety of unfounded properties. An alternative medicine branch, called apitherapy, has developed in recent years, offering treatments based on honey and other bee products for many diseases (Bogdanov et al. 2006). The same as any other natural food, honey can be contaminated by the environment, e.g. by heavy metals, pesticides, antibiotics etc. The use of antibiotics, as well as chloramphenicol (CAP), in apiculture has been known for decades and consequently, their residues can be found in honey (Bogdanov 2006, Reybroeck 2012).

Chloramphenicol is an antibiotic effective against a wide range of gram-negative and gram-positive bacteria in both humans and animals. Due to the resistance, toxicity and safety concerns, it is no longer a first-line agent for any infections in developed nations, with notable exception of topical treatment of bacterial conjunctivitis. The European Union banned CAP use in food-producing animals because of its many serious side effects (e.g. aplastic anaemia, grey syndrome, severe bone marrow depression and hypersensitivity) (Commission Regulation (EC) 1430/94). In Croatia, it was banned in 2003., but the minimum required performance level (MRPL) was set in 2005. at 0.3 μg/kg and now it is completely banned (Official Gazette of the Republic of Croatia 21/2011). Various analytical methods have been reported for determining CAP in honey (Ashwin et al. 2005, Ferguson et al. 2005, Forti et al. 2005, Huang et al. 2006, Pan et al. 2006, Ronning et al. 2006, Rodziewich & Zawadzka 2007, Scortichini et al. 2005, Shen & Jiang 2005, Turnipseed et al. 2002, Verzegnassi et al. 2003) or propolis (Bononi & Tateo 2008) and other biological materials like milk (Agui et al. 2002, Ashwin et al. 2005, Ferguson et al. 2005, Guy et

al. 2004, Huang et al. 2006, Nicholich et al. 2006, Pengov et al. 2005, Perez et al. 2002, Ronning et al. 2006), meat (Ashwin et al. 2005, Fergison et al. 2005, Scortichini et al. 2005, Shen & Jiang 2005, Rocha Siqueira et al. 2009, Ronning et al. 2006), eggs (Huang et al. 2006, Ronning et al. 2006) and sea food (Ferguson et al. 2005, Rocha Siqueira et al. 2009, Shen & Jiang 2005).

Enzyme-linked immunosorbent assay methods (Ferguson et al. 2005, Scortichini et al. 2005, Shen & Jiang 2005, Rocha Siqueira et al. 2009) are very useful for preliminary analyses and screening purposes (mostly because of their easiness) but they can give false compliant results. Any subsequent results require confirmation by other suitable methods. A very sensitive method for determining chloramphenicol is gas chromatography, coupled with electron capture detector (GC-ECD) (Pengov et al. 2005, Shen & Jiang 2005), but this method requires a derivatization step and it is not a confirmative approach. There are some methods like voltametric (Agui et al. 2002), quick and easy capillary electrophoresis, liquid chromatography (Shen & Jiang 2005), with classical detectors (ultraviolet, UV), multi-diode detector (DAD) or fluorescent (FLD) detector which can achieve MRPL and also do not require derivatization for determination of CAP, but these are non-confirmative. For confirmative methods there are few choices. Specifically, GC-MS methods can provide definitive qualitative and quantitative results, but these require a derivatization step (Shen & Jiang 2005). The combination of LC-MS (Ashwin et al. 2005, Bogusz et al. 2004, Forti et al. 2005, Rocha Siqueira et al. 2009, Shen & Jiang 2005, Yibar et al. 2011) offers a rapid, simplified, specific and sensitive alternative to GC-MS methods and removes the need for derivatization reactions.

The present work describes a rapid method for determination and confirmation of CAP in honey, based on liquid chromatography with tandem mass spectrometry (LC-MS/MS) in electrospray negative ion mode. The method was validated according to Commission Decision 2002/657/EC (Commission Decision 2002/657/EC) and performed for the analysis of CAP in samples of Croatian domestic honey in the period from 2005. to 2013. in order to verify our hypothesis of its good quality.

SUBJECTS AND METHODS

Reagents

Analytical standard chloramphenicol (chemical purity 98.5%) was purchased from Dr. Ehrenstorfer (Augsburg, Germany) and chloramphenicol D5 (100 μg/mL in acetonitrile; chemical purity ≥98%) used as an internal standard (IS) was purchased from Cambridge Isotope Laboratories (Andover, MA, USA). For chromatographic analyses and solid phase extraction (SPE), purification and concentration, organic solvents of high-performance liquid chromatography (HPLC) gradient grade methanol and acetonitrile were purchased from Baker (Deventer, Netherlands). An acetate buffer solution 0.01 mol/L was prepared by dissolving p.a. potassium acetate from Kemika (Zagreb, Croatia) and the pH adjusted to 6 via a pH-meter MPC 227, Mettler Toledo GmbH (Giessen, Germany). Samples were diluted with buffer solution and sonicated in ultrasound bath (Branson 1210, Branson Ultrasonics) (Danbury, USA). The 24-port vacuum manifold (Supelco) was used for solid-phase extractions. The honey samples were extracted using SPE cartridges Oasis HLB 6 mL/200 mg, 60 μm. Prior to analysis, all samples were passed through a 0.20 μm disposable filter (Millex-FG, Fluoropore PTFE, Millipore Corp., Sigma - Aldrich Chemie GmbH, Taufkirchen, Germany).

A CAP standard stock solution of 2.0 mg/mL was prepared by dissolving 20 mg CAP in 10 mL of acetonitrile and this solution was diluted in acetonitrile obtaining an intermediate standard solution of 3.0 μg/mL. A CAP working solution of 30 ng/mL was made by diluting a stock solution with acetonitrile. An internal standard of 5D-CAP was prepared by diluting 100 μL of 100 μg/mL stock solution in acetonitrile and then was adequately diluted until a working solution of 30 ng/mL was obtained. All standard solutions were kept at ~4 oC and protected from light for a year.

Equipment

Liquid chromatography analyses were performed on a ZORBAX SB C18 narrow bore column (150x2.1 mm i.d., 3.5 μm) (Agilent Technologies Deutschland GmbH Chemische Analysentechnik, Waldbronn, Germany) using an Finnigan Surveyor (Thermo Electron Corporation) series liquid chromatograph equipped with a binary pump and an autosampler. Data acquisition and quantification were conducted using Excalibur sofware. The column was thermostated at 35°C. Chromatographic separation was performed using gradient elution with 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) starting with a ratio (80:20; v/v) then 0-4 min, 80% —> 25% A; 4-4.5 min at 25% A; 4.5-4.51 min 25% —>80% A; 4.51-6.5 min 80% A. The flow was set at 0.3 mL/min and the injection volume was 25 μL. Under these conditions, the retention time of CAP and 5D-CAP was observed at 3.15 min.

Mass spectrometry analyses were performed on a Finnigan TSQ Quantum Ultra EMR triple stage quadrupole mass spectrometer (Thermo Electron Corporation) equipped with a heated-electrospray interface (HESI). The electrospray capillary temperature was 350°C and the capillary voltage was 4500 V. Nitrogen was used as a collision gas. MS detection was performed in negative mode using Multiple Reaction Monitoring (MRM). The monitored ion for CAP was m/z 321, and the product ions used for quantification were m/z 257, 194, and 152 and for 5D-CAP as internal standard monitored ion was m/z 326 and the product ions used for quantification were m/z 157 and 262. The scan time for each transition reaction was 500 ms with scan width 1.0 m/z. The MRM transition and their collision energies are shown in Table 1.

Table 1. Multiple reaction monitoring (MRM) transitions monitored for chloramphenicol (CAP) and internal standard 5D-CAP (IS) and their collision energies

Compound	Precursor ion m/z	Product ion m/z	Collision energy (eV)
CAP	321	152	20
CAP	321	194	19
CAP	321	257	12
5D-CAP (IS)	326	157	20
5D-CAP (IS)	326	262	12

Honey samples

Commercial domestic honey samples were randomly collected from all districts of Croatia during 2005.–2013. Honey samples were of different varieties, but mostly acacia (32%), flower (17%), chestnut (9%), linden (8%), honeydew (5%), sage (5%), lavender, fruit honey and honey with some substances added, including lemon, cherry, etc. Some of the samples were collected by sanitary inspection and others were analysed from distributors. Prior to analyses, all samples were stored in dark and dry places at ambient temperature (around 22°C) and in their original containers.

Honey sample preparation

The homogenized honey samples (5.0±0.01 g) were weighed in 200 mL beakers and fortified with 50 µL of working internal standard 5D-CAP and diluted with 10.0 mL acetate buffer. The samples were well mixed and 15 min sonicated at ultrasound bath and then purified and concentrated using HLB Oasis SPE cartridges. After preconditioning the cartridges by flushing 3 mL of methanol, 3 mL of water and 3 mL of acetate buffer, the whole sample was allowed to pass through the bed with suction. Purification was done by flushing 3 mL buffer and 6 mL of water.

Different extraction protocols were assayed using various eluting solvents, various volumes of solvent and different SPE columns (Krivohlavek et al. 2005). The best results were obtained with 2 mL of acetonitrile. Acetonitrile was evaporated until dry under a stream of nitrogen using a water bath at 35°C. The dry residue was redissolved in 0.5 mL mobile phase acetonitrile: water (20:80, v/v) and then filtered through a 0.20 µm disposable filter. Twenty-five µL was injected into LC-MS/MS.

Calibration curves at six concentrations levels were prepared by spiking blank honey samples with CAP at the following concentrations: 0.0 (blank samples), 0.10, 0.30, 0.50, 1.00 and 3.00 µg/kg. A fixed amount of an internal standard 5D-CAP was added to all the samples at concentration 0.30 µg/kg. The calibration curves were obtained relating to a ratio of CAP area/CAP-D5 area with CAP mass ratio in µg/kg. A calibration curve with standards was made every day.

RESULTS

For the purpose of the honey market control safety, especially domestic ones, according to banned chloramphenicol in food-producing animals in the European Union, the LC-MS/MS method was performed and validated.

A gradient LC-ESI/MS/MS method with an internal standard was developed to separate, quantify and confirm the presence of CAP in honey. A MRM procedure was applied. The three transitions were monitored m/z 321 —> m/z 257, m/z 321 —> m/z 194, m/z 321 —> m/z 152. According to Commission Decision 2002/657/EC for the confirmation of banned substances, a minimum of four identification points is required (Commission Decision 2002/657/EC). The four identification points can be obtained using LC-MS/MS with one precursor and two product ions. The presented research method detected 3 product ions and so the performance criteria for confirmation were fulfilled. Method validation was performed using both standard solution and spiked-honey samples. The method was validated according to the criteria of Commission Decision 2002/657/EC (Commission Decision 2002/657/EC). According to these criteria, validation included selectivity, linearity, precision (within-days and between-days), accuracy, decision limit (CCα), detection capability (CCß), robustness, sensitivity, stability and measurement uncertainty.

The selectivity of the method was checked by the preparation and analysis of blank and spiked honey samples from different origins (acacia, chestnut, linden and flower) to verify the absence of potential interfering compounds in honey. No interference was observed around CAP retention times in honey samples. Figure 1 show MRM chromatograms of a blank honey sample, same blank honey sample with the addition of 0.30 µg/kg CAP and appropriate standard solution, respectively.

The linearity response was studied using seven working standards injected three times, covering the entire working range of 0.5–50 ng/mL containing a fix amount of 5D-CAP (3.0 ng/mL). Chloramphenicol standard solution/internal standard peak area ratio was calculated versus chloramphenicol amount in ng/mL. Calibration curve was built using blank honey samples with the addition 0.00–3.00 µg/kg CAP as shown in Figure 2. For both curves, the linear correlation coefficient was greater than 0.99.

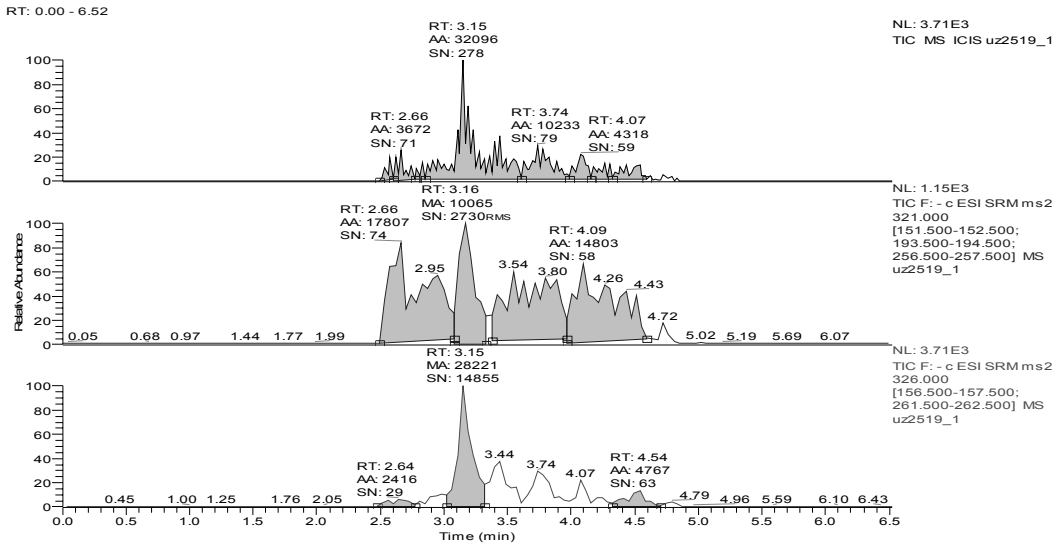

Fig. 1a. Liquid chromatography tandem mass spectrometry (LC-MS/MS) chromatogram of blank acacia honey extract

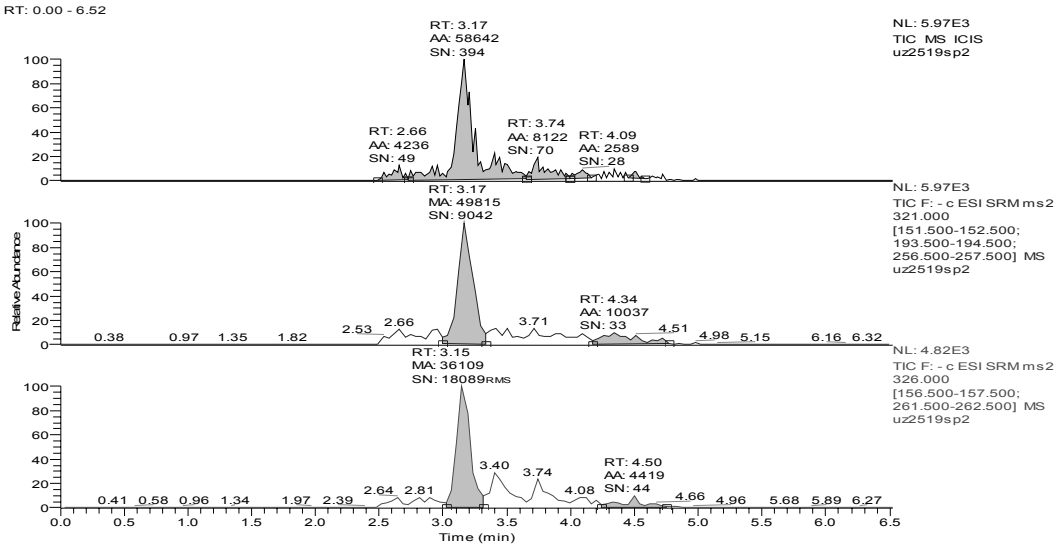

Fig. 1b. Liquid chromatography tandem mass spectrometry (LC-MS/MS) chromatogram of blank acacia honey sample with the addition of 0.30 µg/kg chloramphenicol (CAP)

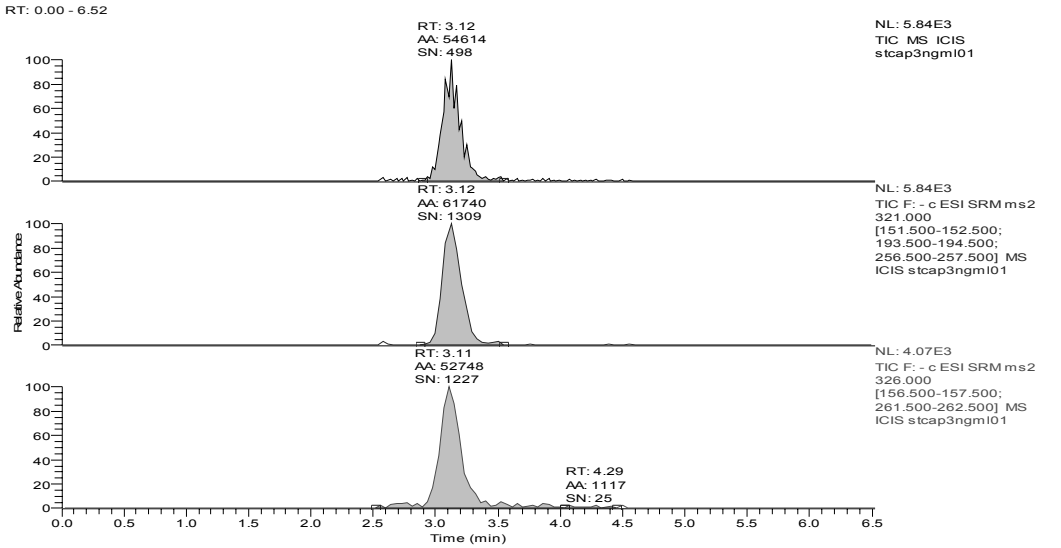

Fig. 1c. Liquid chromatography tandem mass spectrometry (LC-MS/MS) chromatogram in standard solution (3.0 ng/mL)

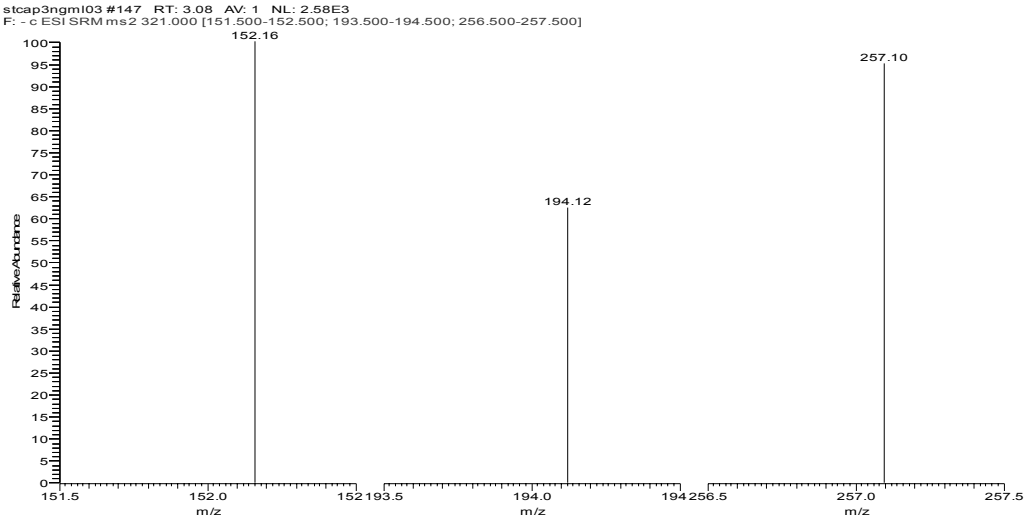

Fig. 1d. Mass spectrometry spectra of three multiple reaction monitoring (MRM) transitions monitored for CAP in standard solution

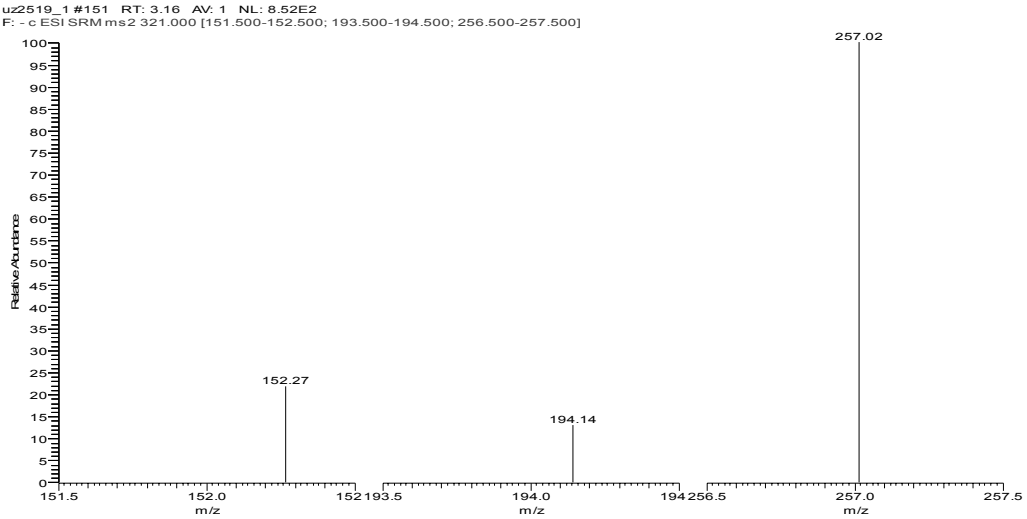

Fig. 1e. Mass spectrometry spectra of three multiple reaction monitoring (MRM) transitions monitored for CAP in blank sample

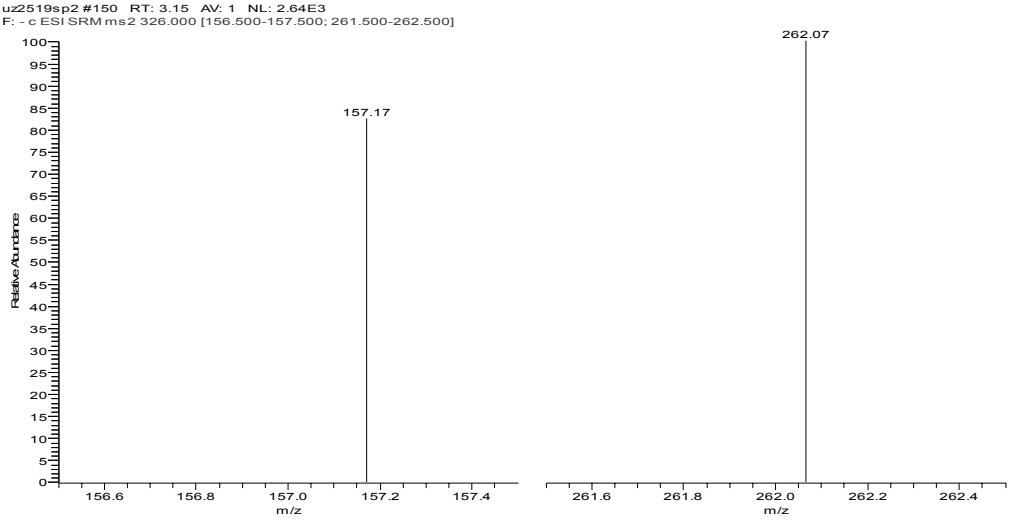

Fig. 1f. Mass spectrometry spectra of two MRM transitions monitored for internal standard 5D-CAP

Figure 1. Liquid chromatography tandem mass spectrometry (LC-MS/MS) chromatograms of blank acacia honey extract (a), blank acacia honey sample with the addition of 0.30 μg/kg chloramphenicol (CAP) (b) and appropriate standard solution (3.0 ng/mL) (c) with three multiple reaction monitoring (MRM) transitions monitored for CAP in standard solution (d) and in blank sample (e) and two MRM transitions monitored for internal standard 5D-CAP (f)

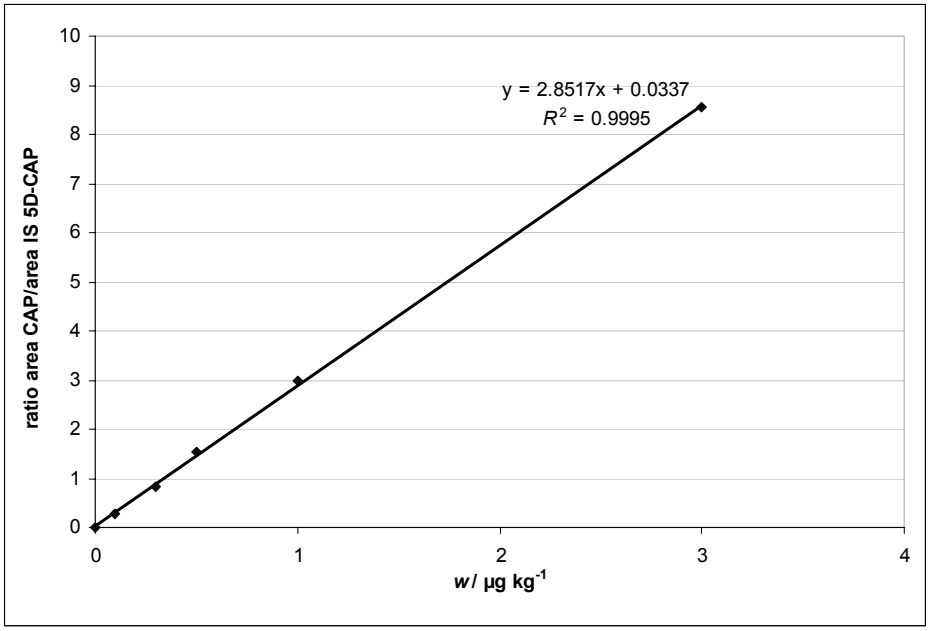

Figure 2. Linearity of calibration curve using blank honey samples with the addition of 0.00–3.00 µg kg^{-1} chloramphenicol (CAP) and with 0.30 µg/kg of internal standard 5D-CAP added at all six concentration levels

Table 2. Precision and accuracy for chloramphenicol (CAP) determination in spiked acacia honey samples

Precision	Spiked acacia honey samples		
Fortification levels (µg/kg)	0.10	0.30	0.50
Average (µg/kg) (n=9)	0.11	0.29	0.43
Within-day precision, RSD (%)	6.90	5.70	6.90
Recovery (%)	113	98	87
Between-day precision, RSD, (%), (n=3x9)		9.00	

DISCUSSION

Precision (within-day) and accuracy (recovery) were calculated from the analysis of blank honey spiked at three levels: one at MPRL and two around the MPRL (0.10, 0.30, and 0.50 µg/kg, respectively) of CAP. Nine replicates were obtained for each concentration. Precisions (within-day) were found that satisfied the three levels studied and RSD values were 5.7–6.9%. The recovery (trueness) was calculated by comparing the measured concentration to the spiked concentrations. The average recovery was in the range of 87–113% for all levels. Precision (between-day) was calculated in spiked samples at 0.30 µg/kg on three different days (3×9). The relative standard deviation was 9%. The precision and accuracy are presented in Table 2.

The stability of standard solutions was also investigated. Working standard solutions of CAP (25 pg/µL) were prepared on the same day from the stock solution (kept in dark and around 4°C) prepared over a year and then analysed. The relative standard deviation was 11%. The stability of the working standard solutions and prepared samples were also investigated. Standard solutions and prepared samples with standard added at 0.30 µg/kg were tested every second day for a ten-day period and the results showed that RSD values were 9.7 and 11.4% respectively. For a test of robustness, the matrix effect was assessed. Nine replicates of different types of honey (acacia, chestnut, linden and flower) were spiked at a limit of quantification of 0.30 µg/kg and analysed (Table 3).

The revised criteria also introduce the decision limit (CCα) and detection capability (CCß) to replace the limit detection and quantification, respectively. In accordance with the Commission Decision 2002/657/EC, more than 20 representative blank samples with internal standard added were analysed to determine CCα and CCß. The values of CCα and CCß were 0.09 and 0.12 µg/kg, thus below the MRPL set at 0.3 µg/kg by the EU amending Decision 2002/657/EC (Commission Decision 2002/657/EC).

The validated method, LC-MS/MS was used for routine analysis of CAP in Croatian honey samples. It is relatively fast, but some literature data showed that using molecularly imprinted polymers (MIPs) or magnetic MIPs (MMIP) may overcome multistep pretreatment, time and labour work of purification and extraction of complex matrix as it is honey, prior LC-MS/MS analysis (Boyd et al. 2007, Chen & Bin 2013).

Table 3. Matrix effect for chloramphenicol (CAP) determination in different honey samples (acacia, chestnut, linden and flower) spiked at 0.30 μg/kg

Type of honey	Acacia (n=9)	Chestnut (n=9)	Linden (n=9)	Flower (n=9)	All (n=36)
Average recovery (%)	99	94	100	113	102
Standard deviation (%)	5.7	2.4	6.1	4.0	8.5
Coefficient of variation (%)	5.8	2.6	6.1	3.5	8.4

CAP residues were analysed in 280 samples but only detected above the CCα in three samples using this procedure. One sample was acacia honey from 2005. and the other from 2006. and the third was from 2008. with 1.6 μg/kg, 1.8 μg/kg and 0.54 μg/kg, respectively. Since 2008., no honey samples with chloramphenicol were detected above CCα (Table 4) showing good quality of domestic honey. To the best of our knowledge, this is the first time that such investigation has been done on the Croatian market.

Table 4. Analysed honey samples collected randomly from all Croatian districts present at Croatian market in period between 2005-2013

Year	Total number of analysed honey samples	Number of non compliant honey samples	% of non compliant honey samples
2005	9	1	11.1
2006	51	1	2.0
2007	16	0	0
2008	10	1	1.00
2009	37	0	0
2010	47	0	0
2011	20	0	0
2012	31	0	0
2013	59	0	0
2005-2013	280	3	1.1

It is known that the presence of xenobiotics, antibiotic residues in honey may harm its quality and constitute a danger to human health. Safety of food and feed is the one of the main objective in consumer health policy, and CAP is completely banned in food producing animals within EU due to its toxicity in humans (Commission Regulation (EC) 1430/94), but not in some countries outside of Europe (for example Asia). Therefore, it was necessary to develop a sensitive and rapid method as it is presented in our study to control and monitor CAP residues in honey on European market even a decreased trend was noted also by European Rapid Alert System for Food and Feed (RASFF) (European Rapid Alert System for Food and Feed - Reports and Publications).

Furthermore, honey consumption is very high in developed countries, where domestic production does not always meet the market demand. In the EU, which is both a major honey importer and producer, the annual consumption per capita varies from medium (0.3-0.4 kg) in Italy, France, Great Britain, Denmark and Portugal to high (1-1.8 kg) in Germany, Austria, Switzerland, Portugal, Hungary and Greece, while in countries such as the USA, Canada and Australia the average per capita consumption is 0.6-0.8 kg/year. The major honey exporting countries, China and Argentina, have small annual consumption rates of 0.1-0.2 kg per capita (Bogdanov et al 2008). According to the data of Statistical Yearbook 2013 of the Republic of Croatia annual average of honey per household member was 1.1 kg in 2011. and 1.2 kg in 2010. (Statistical Yearbook of the Republic of Croatia 2013). The consumption grew from 0.3 kg to approximately 1 kg in the period of 10 years (Statistical Yearbook of the Republic of Croatia 2003, Statistical Yearbook of the Republic of Croatia 2013). Additionally, it was showed that honey has a variety of positive nutrition and health effects, if consumed at higher doses of 50 to 80 g per intake (Bogdanov et al. 2008). But, health benefits of popular food could be diminished or even become disadvantage if it contains CAP residues. It is not only because of harm effect of CAP as a well known bone marrow depressant, but also because of possible interactions of CAP and some prescribed conventional drugs (Baxter K & Preston CL 2008). CAP is also a known enzyme inhibitor and could grow up level of many drugs by reducing their metabolism and thus caused toxicity. Some well documented and established interactions of clinical importance were between CAP and tolbutamide, phenytoin, iron compounds and vitamin B12. So, the result of interaction could be acute hypoglycaemia, phenytoin toxicity and opposes the treatment of anaemias with iron or B12, respectively, depending of the dose of the two (Baxter K & Preston CL 2008).

Since, consumption of honey and various honey products constantly grows, safety of products and consumer's health becomes of the biggest importance, and therefore routine control of the market by validated and confirmative method of forbidden CAP residue is necessity.

CONCLUSIONS

Chloramphenicol residue analysis of various honey samples (acacia 32%, chestnut 9%, linden 8%, flower 17% others 34%) from Croatia in the year period of 2005. to 2013. showed very good quality. Only three of 280 (1.1%) honey samples were non compliant having chloramphenicol above CCα. All non compliant samples were acacia ones. Presented LC-MS/MS method

for determining chloramphenicol in various honey samples is fast, robust and confirmative. The sample preparation is simple and has good precision and recoveries. Thus is appropriate for routine honey analyses of CAP residue. The validation results are in accordance with the performance method criteria of the European Commission Decision 2002/657/EC.

Acknowledgements: None.

Conflict of interest : None to declare.

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Psychiatria Danubina, 2014; Vol. 26, Suppl. 3, pp 546-551 *Original paper*

MELITOCOCCOSIS IN THE REPUBLIC OF CROATIA

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SUMMARY

Background: *Melitococcosis is one of the most widespread zoonoses worldwide. In the period from 2009 to 2013, comprehensive melitococcosis testing was conducted in the Republic of Croatia.*

Methods and results: *During the testing, the Rose Bengal test was applied to 344019 blood samples of sheep and goats, and positive reactions were confirmed in 1143 (0.3%) of samples. The complement fixation test (confirmatory test) was conducted on 43428 samples, with positive reactions confirmed in 768 (1.8%) of samples. The organs and tissues of 336 sheep and goats were inspected bacteriologically, and Brucella sp. was isolated in 15 (4.5%) of samples. Positive serological and bacteriological reactions were confirmed in the Karlovac, Lika-Senj and Split-Dalmatia Counties. Bacteriological and molecular techniques (Bru-up/Bru-low and Bruce-Ladder) in isolates proved the presence of Brucella melitensis biovar 3.*

Conclusion: *On the basis of this study, it can be concluded that Croatia has a favourable situation concerning the infection of ruminants with B. melitensis, and that ongoing controls of the disease are necessary.*

Key words: *melitococcosis - Brucella melitensis – ruminants - serological and bacteriological tests - Republic of Croatia*

* * * * *

INTRODUCTION

Melitococcosis or brucellosis is a chronic infectious disease of sheep and goats caused by the species Brucella (B.) melitensis. It is one of the most widespread zoonoses worldwide. Its appearance has a great influence on human and animal health, economic development and the agriculture and tourism of that country. It is particularly widespread in sheep and goats in the Mediterranean region. It is considered to be one of the most dangerous diseases transmitted from animals to humans. According to the Center for Disease Control and Prevention (CDC; Atlanta, USA), brucellosis falls within the B category of diseases due to its potential for use as a biological weapon (Saleem et al. 2010). According to the assessment of the World Health Organization (WHO), some 500000 cases of brucellosis in humans is reported each year, though this figure may be up to 25 times higher in reality (Pappas et al. 2006, Bosilkovski 2013).

In Croatia, limited cases of infection appear in sheep and goat flocks, and such cases were recorded in 2004, 2005, 2008 and 2010 (Cvetnic et al. 2006, Spicic et al. 2010, 2013). The distribution of brucellosis caused by B. melitensis in Bosnia-Herzegovina indicates the constant threat of the spread of the disease into Croatia (Dautovic-Krkic 2006, Velic & Bajrovic 2006, Zvizdic et al. 2006, Punda-Polic & Cvetnic 2006). In Serbia, this disease appears sporadically, and usually in the southern parts of the country (Zutic et al. 2013). In Slovenia, the disease has been eradicated since 1951 (Krt & Socan 2013). In Italy, Spain, Greece, Turkey and some Balkan countries (Macedonia, Albania and Kosovo), the disease is present, and various brucellosis eradication programmes are ongoing (Pappas et al. 2006, Godfroid & Kasbahrer 2002, Taleski et al. 2002, Pappas 2010).

This paper gives an overview of the distribution of melitococcosis in the Republic of Croatia in the period from 2009 to 2013. Bacteriological and molecular techniques were used to prove and confirm the species Brucella sp.

SUBJECT AND METHODS

Serological research

In the investigated period from 2009 to 2013, a total of 344019 blood samples of sheep and goats were tested serologically using the Rose Bengal test (RBT) for brucellosis (B. melitensis) at the Croatian Veterinary Institute. In addition, 43428 samples were tested using the complement fixation test (CFT). The blood samples of sheep and goats were collected from the territories of 20 counties and the City of Zagreb (Table 1).

The serological methods prescribed in the OIE Manual of Standards for diagnostic test and vaccines, 2009 were used for the serological diagnosis of brucellosis. The Rose Bengal test was used as a screening test to detect brucellosis (B. melitensis) in sheep and goats, and the complement fixation test was used as a confirmation test. For the RBT, an antigen produced at the Croatian Veterinary Institute Zagreb was used, and for the CFT, we used an antigen produced at the Institute Pourquier Montpelier - France. The results were interpreted according to the manufacturer's instructions or the test instructions.

Table 1. Results of serological testing of blood samples of sheep and goats for brucellosis in the period from 2009 to 2013

Year	2009		2010		2011		2012		2013	
County	RBT (+)	CFT (+)	RBT (+)	CFT (+)	RBT (+)	CFT (+)	RBT (+)	CFT (+)	RBT (+)	CFT (+)
Bjelovar-Bilogora	2357 (1)	71	903 (8)	56	1083 (2)	6	15655 (64)	107	17140 (101)	133
Brod-Posavina	338	0	350	0	140	0	291	0	213	0
Dubrovnik-Neretva	393	0	84	0	130	0	51	0	24	0
Istria	937 (1)	0	474 (1)	1	508	0	7181	0	7399	0
Karlovac	25651 (19)	24818 (5)	6547 (9)	6019	550	0	2538	0	2874 (7)	7
Koprivnica-Križevci	491	24	501 (8)	12	198	1	2091 (4)	6	1655 (13)	16
Krapina-Zagorje	120	0	127 (1)	1	58 (1)	1	227	0	317	2
Lika-Senj	407	24	4368 (283)	3975 (342)	5986 (8)	5486 (1)	3990	0	4285 (73)	107 (79)
Međimurje	690	148	245	0	86	0	3155 (7)	15	3019 (6)	15
Osijek-Baranja	1824	0	1543	0	542 (2)	5	1709 (1)	1	2474 (3)	4
Požega-Slavonia	1080	0	416	19	646	0	4199 (1)	1	3337 (8)	8
Primorje-Gorski Kotar	1351	1	750	0	967	0	1286 (1)	1	1651	0
Sisak-Moslavina	1086 (6)	517	384	149	472	5	892 (3)	3	796 (6)	6
Split-Dalmatia	33962 (258)	657 (243)	35136 (114)	223 (98)	10516 (13)	15	3347 (6)	9	9558 (17)	20
Šibenik-Knin	2571	1	4179 (1)	2	1434	0	2008 (1)	1	1863	0
Varaždin	761	0	269	0	168	0	4987 (24)	46	4605 (6)	5
Virovitica-Podravina	1391	0	506	0	487	0	8156 (1)	3	7710 (6)	7
Vukovar-Srijem	490	1	718 (3)	198	346 (3)	93	338 (2)	2	239	0
Zadar	2524	8	380	0	1482	0	23332 (11)	16	22920 (55)	67
Zagreb	924	1	311	0	259 (7)	3	544	0	742	0
City of Zagreb	0	0	0	0	0	0	801	0	949	0
Total	79348 (284)	26271 (248)	58064 (420)	10643 (440)	26059 (36)	5612 (1)	86778 (102)	211 (0)	93770 (301)	691 (79)

RBT – Rose Bengal test, CFT - complement fixation test, + - number of positive samples

Bacteriological testing

During the investigated period, animals that were serological positive for brucellosis were brought in for slaughter. Samples of lymph nodes (parotid, submandibular, retropharyngeal, portal, subiliac, mesenterial, supramammary), liver, spleen and reproductive organs (uterus and testes) were taken from available animals or from aborted foetuses delivered to the laboratory for bacteriological testing. Samples for bacteriological testing were taken from 26 sheep, goats or cow from Bjelovar-Bilogora County, 1 from Dubrovnik-Neretva County, 11 from Istria County, 22 from Karlovac County, 7 from Krapina-Zagorje County, 51 from Lika-Senj County, 2 from Osijek-Baranja County, 11 from Pozega-Slavonia County, 15 from Primorje-Gorski Kotar County, 19 from Sisak-Moslavina County, 41 from Split-Dalmatia County, 40 from Sibenik-Knin County,

2 from Varazdin County, 6 from Virovitica-Podravina County, 9 from Vukovar-Srijem County, 30 from Zadar County, 39 from Zagreb County and 4 samples from the area of the City of Zagreb. In this period, no samples were submitted from Međimurje County, Brod- Posavina County and Koprivnica-Krizevci County. During the survey period, samples from 336 sheep and goats from 16 counties and the City of Zagreb were analysed.

Several grams of delivered and examined materials (testes, uterus, placenta, aborted foetuses and lymph nodes) were inoculated on selective agar and on blood agar, Brucella agar and modified selective Farell agar. Agars with inoculated materials were incubated at normal atmosphere conditions at a temperature of 37°C with the addition of 5–10% CO2. Colony growth was observed daily, and was usually visible after 3–7 days. Isolates were identified on the basis of colony morphology (small, convex, transparent, rough (R), growth with CO2, production of H2S, growth on medium with the addition of 20µg/ml thionine and basic fuchsine and agglutination with monospecific antiserums (Alton et al. 1988, Corbell et al. 1983, OIE Manual 2009).

Molecular analysis of Brucella sp.

The isolation of DNA from isolates was conducted using QIAcube system (QIAGEN, Hilden, Germany). Brucella sp. in isolates was proven by amplification of the part of the gene that codes for the synthesis of the BCSP-31 protein (Bricker & Halling 1994, Serpe et al. 1999). The size of the amplification product was 443 bp (base pairs). We used the primers BRU-UP (GGG CAA GGT GGA AGA TTT) and BRU-LOW (CGG CAA GGG TCG GTG TTT) (Invitrogen, USA).

The Bruce Ladder test was used to prove which Brucella species was present, including the referent strains (B. abortus S19, B. abortus RB51 and B. melitensis Rev1). Eight pairs of primers were used per reaction mixture. Members of individual species were differentiated on the basis of the characteristic mutations, insertions and deletions in their genomes (Lopez-Goni et al. 2008). The amplification products were analysed using capillary electrophoresis on the QIAxcel system (QIAGEN, Hilden, Germany) with 100-3000 bp size marker (QIAGEN, Hilden, Germany).

Statistical analysis was performed using the statistical program Stata 13.1 (Stata Corp., USA). Numerical data for the seroconversion tested using the Rose Bengal test were compared among years and among regions (Slavonia and Baranja, central Croatia and Lika, Istria, Primorje and Dalmatia) using the chi-squared and Fisher exact tests.

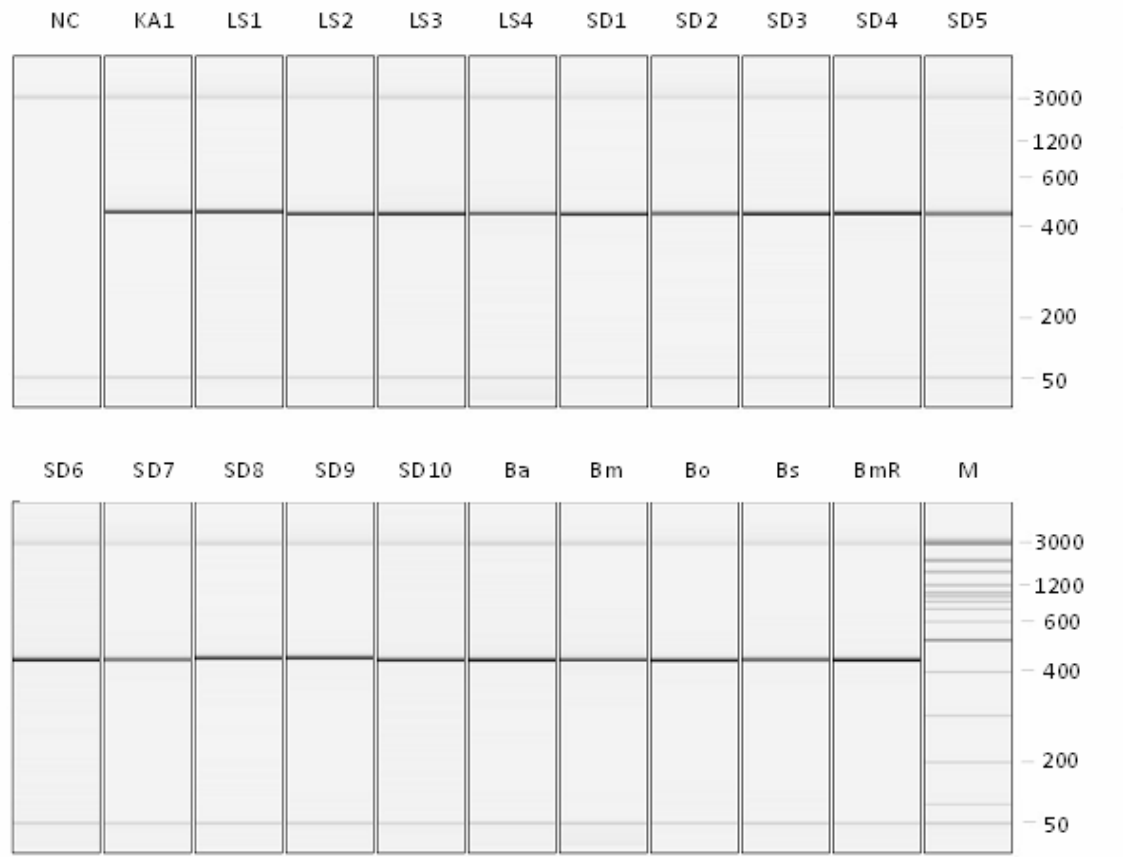

Figure 1. Identification of Brucella genus using Bru-up/Bru-low PCR method20. NC – negative control, KA1 – Brucella melitensis isolate from Karlovac County, LS1- LS4 - Brucella melitensis isolates from Lika-Senj County, SD1-SD10 - Brucella melitensis isolates from Split-Dalmatia County, control strains (Ba – Brucella abortus 544, Bm – Brucella melitensis 16M, Bo – Brucella ovis 63/290, Bs – Brucella suis 1330, BmR – Brucella melitensis Rev1), M – size marker 50 – 3000 bp (Qiagen)

RESULTS

Serological tests

During the survey period from 2009 to 2013, the RBT screening test was applied to 344019 blood samples, with positive reactions confirmed in 1143 (0.3%) of blood samples of sheep and goat. The CFT method was used to test 43428 samples, with positive reactions confirmed in 768 (1.8%) of blood samples. Positive reactions were most often found in Karlovac, Lika-Senj and Split-Dalmatia Counties (Table 1).

The observed differences in the incidence of positive results of the Rose Bengal test between individual regions were statistically significant in all years ($p<0.0001$) except 2011 ($p=0.09$). The observed differences in the incidence of positive results of the Rose Bengal test between years were statistically significant ($p<0.0001$).

Organ and tissue samples of 336 sheep and goats were examined bacteriologically, and brucellosis was isolated in 15 (4.5%) of samples. Positive bacteriological analysis was confirmed in Karlovac County (1 isolate), Lika-Senj County (4 isolates) and in Split-Dalmatia (10 isolates). During 2009, 5 isolates were isolated (Karlovac, Split-Dalmatia Counties) and in 2010, 9 isolates were obtained (Lika-Senj and Split-Dalmatia Counties), while in 2013, only 1 isolate was found (Lika-Senj County). In 2011 and 2012, no brucellosis isolates were isolated from the tested samples.

Following the isolation and identification of Brucella sp. using classical bacteriological procedures, identification using the polymerase chain reaction (PCR) method was carried out. All 15 isolates obtained from sheep, goats and one bovine sample were proven to belong to the genus Brucella sp., i.e. the presence of the gene for the protein BCSP-31 was proven (Figure 1).

Upon confirming that all investigated samples belonged to the genus Brucella, the Bruce ladder test, a multiplex PCR assay with eight primers, was used to confirm that all 15 isolates belonged to the species B. melitensis. Samples were differentiated on the basis of the combination, presence or absence of amplicons of different sizes: 1682, 450, (1320), 1071, 794, 587, 272, 218 and 152 bp (Figure 2).

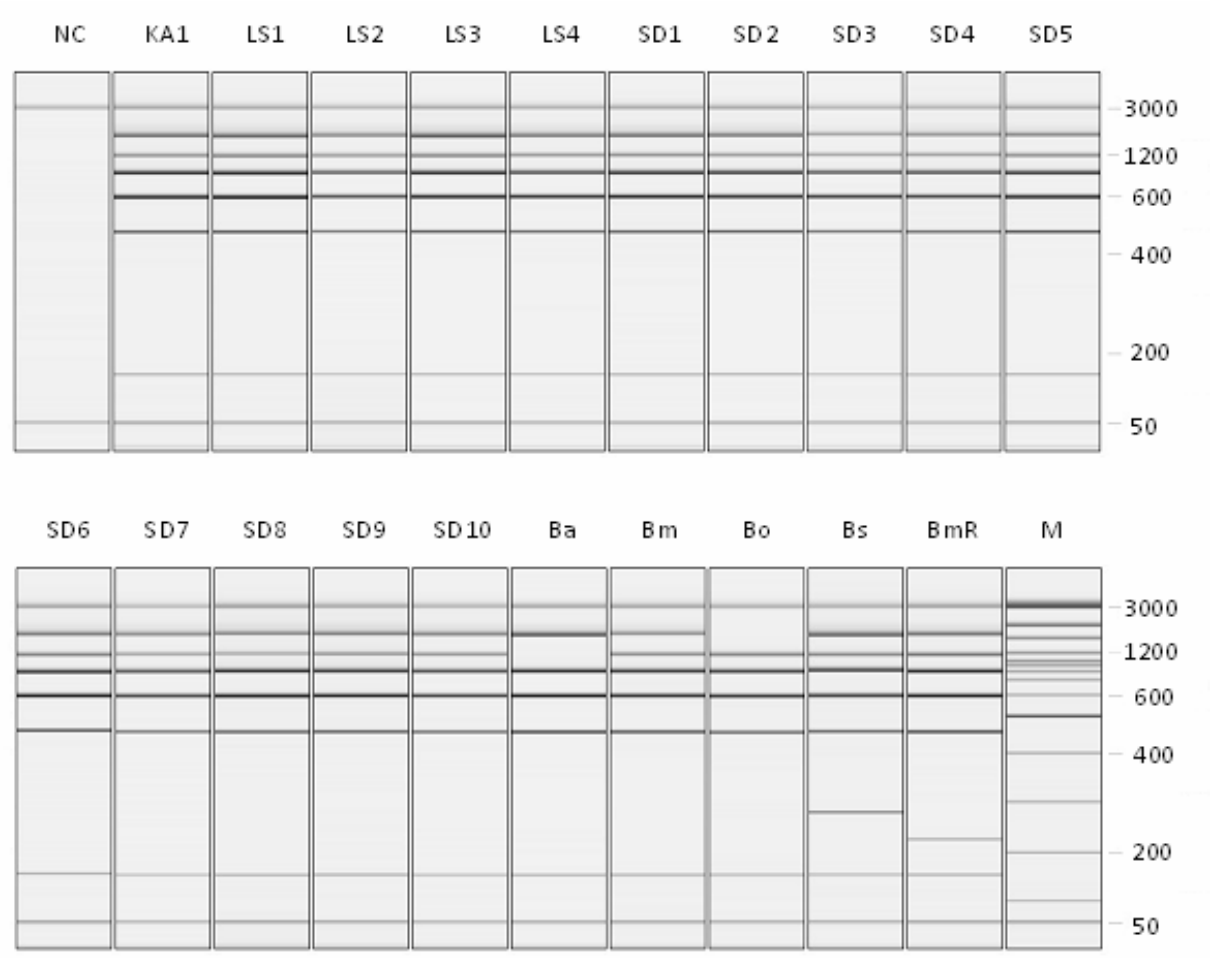

Figure 2. Identification of Brucella species using Bruce-ladder multiplex PCR method21. NC – negative control, KA1 – Brucella melitensis isolate from Karlovac County, LS1- LS4 - Brucella melitensis isolates from Lika-Senj County, SD1-SD10 - Brucella melitensis isolates from Split-Dalmatia County, control strains (Ba – Brucella abortus 544, Bm – Brucella melitensis 16M, Bo – Brucella ovis 63/290, Bs – Brucella suis 1330, BmR – Brucella melitensis Rev1), M – size marker 50 – 3000 bp (Qiagen)

DISCUSSION

In recent years, systematic work has virtually succeeded in eradicating this disease in Croatia; however, despite all efforts, it still survives in varying intensity. In order to prevent and stop outbreak of this disease in humans and animals from the very early stages, constant supervision over animal health is imperative. Brucellosis in humans is first found in people professionally tied to livestock (breeders, veterinarians, farmers) than in those consuming the products (milk, cheese) of infected animals.

During a survey from the period of 2009 to 2013, the RBT screening test was used to test 344019 blood samples, and positive reactions were confirmed in 1143 (0.3%) of blood samples of sheep and goats. The CFT method was applied to 43428 samples, and positive reactions were obtained in 768 (1.8%) of blood samples. Positive serological reactions and bacteriological tests were found in Karlovac, Lika-Senj and Split-Dalmatia Counties. Croatia is one of the rare Mediterranean countries with a favourable status with the appearance of melitococcosis. All cases of the appearance of the disease to date have appeared in flocks and people living in areas directly along the border with Bosnia-Herzegovina (BiH), and it is believed that the illegal import of animals from BiH is the main source of infection with B. melitensis (Cvetnic et al. 2006). This was also evident from earlier studies by Spicic et al. (2010), where melitococcosis appeared in the same bordering counties (Karlovac, Lika-Senj and Split-Dalmatia) (Spicic et al. 2010). In the literature, cases of illegal imports of infected animals have been reported in various areas, from Albania into north-western Greece, from Turkey into southern Bulgaria, and from Mexico into the southern USA (Pappas et al. 2006, Russo et al. 2009).

Several larger outbreaks of melitococcosis have occurred in Croatia. The first was described in Istria in 1947, when more than 300 people became infected with melitococcosis. The last known case of the disease in a human was reported in 1954, and in sheep and goats in 1961 (Karlovic 2000, Terlevic 2006). In 1990, an outbreak of melitococcosis was reported in Istria, and in 1991 and 1992 in the Varazdin and Bjelovar regions (Cvetnic et al. 2001). According to the data of the Croatian Public Health Institute, 7 humans were reported to have clinical symptoms of brucellosis in 1990, 17 patients in 1991, 12 patients in 1992 and 4 patients in 1993. During 2004, an outbreak caused by B. melitensis was reported in Split-Dalmatia County. Positive reactions were confirmed in 372 sheep and goats and 5 dogs in 5 flocks, and veterinary measures were employed to destroy 1567 sheep and goats. During the outbreak, clinical symptoms of brucellosis were confirmed in 4 people. Later, a case of brucellosis in a human was confirmed in Dubrovnik-Neretva County (Metkovic), and brucellosis was recorded in several sheep and goat flocks during 2005 (Cvetnic et al. 2006, Punda-Polic & Cvetnic 2006). Pappas (2010) described the spread of the disease on the Balkan Peninsula, and stated that melitococcosis is present in Greece, Turkey, Macedonia, Albania, Kosovo and southern Serbia, and it later spread to Bosnia-Herzegovina, and from Bosnia-Herzegovina into Croatia (Pappas 2010). Dautovic-Krkic (2005) stated that in the period from 2000 to 2005, there were 245 cases of brucellosis reported in people in Bosnia-Herzegovina (Dautovic-Krkic 2006). Velic & Bajrovic (2005) and Cvetnic et al. (2008) stated that cases of brucellosis in animals were recorded in all cantons of the Federation of Bosnia-Herzegovina, with 335 cases of human infections (Velic & Bajrovic 2006, Cvetnic et al. 2008).

The European Union strategy for the control and eradication of the disease includes testing and slaughter in low incidences countries (Croatia). In countries with moderate incidences, also vaccination of replacement females is carried out, while in cases of high prevalence, massive vaccinations are implemented (Greece, certain regions of Spain and Portugal, Bosnia-Herzegovina). Through the implementation of joint policies of control and eradication of the disease, there has been a reduction of infections in humans, from about 4000 in 1999 to 400 in 2011.

Every country has its own legislation on the control of the disease, trade in livestock, marking, etc., and all of these regulations are more or less based on the legislation of the European Union. However, the strategy to eradicate the disease differs between countries, based largely on the situation with brucellosis in the country, the opportunities, and other socio-political and financial circumstances that are important for the implementation of comprehensive measures to control and eradicate brucellosis. There are constant threats, including the fact that it is always possible the disease will emerge in a country resulting from a reduction in supervision due to an underestimation of the incidence of the disease. Terminations of programs to vaccinate sheep and goats result in flare ups of the disease as do weak border controls and imports of infected animals into disease-free countries. Ultimately, wild ruminants also represent sources of brucellosis. For example, France has officially been a brucellosis-free country in ruminants since 2005; however, brucellosis caused by the species B. melitensis was proven in alpine ibex (Capra ibex) in the French Alps. Subsequent research and molecular testing proved that the strain in humans and goats and domesticated ruminants was identical to that in the ibex (Mick et al. 2014).

Based on this survey, it can be concluded that Croatia has a favourable situation with regard to the infection of humans with B. melitensis, although there is the ongoing threat of the entry of infections from the territory of BiH into Croatia, which has been proven in this study. The appropriate strategies have proven to be efficient, and constant supervision and control of the disease is mandatory even in disease-free regions, and also in the Republic of Croatia.

Acknowledgements: None.

Conflict of interest : None to declare.

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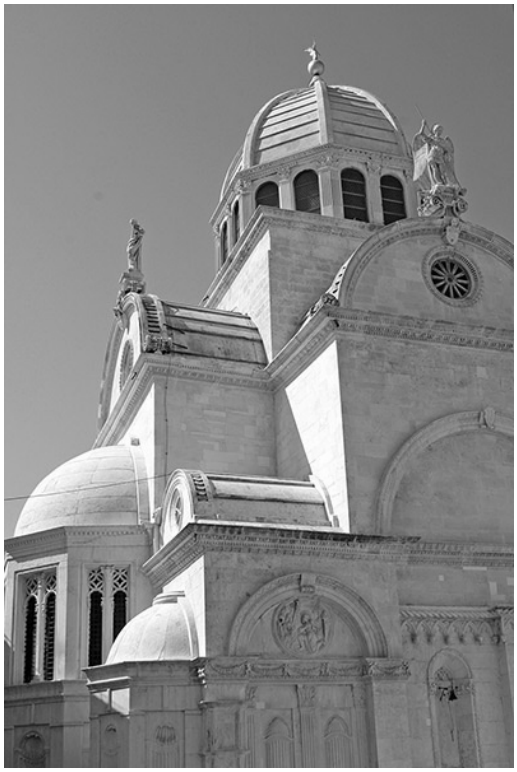

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