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Acta Medica Academica

Journal of Department of Medical Sciences
of Academy of Sciences and Arts of Bosnia and Herzegovina

ISSN 1840-1848 (Print) Volume 43 Number 1 May 2014 ISSN 1840-2879 (Online)

Online First www.ama.ba

Acta Medica Academica

Contents
2014 Vol. 43, No. 1

Acta Medica Academica

www.ama.ba

AIMS AND SCOPE

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SUBSCRIPTION

Acta Medica Academica is published semi-annually. The annual subscription fee is € 50 outside of Bosnia and Herzegovina.

PUBLISHER CONTACT INFORMATION

Academy of Sciences and Arts of Bosnia and Herzegovina, Sarajevo, Bosnia and Herzegovina. Contact person: Husref Tahirović, E-mail: husref.tahirovic@untz.ba

COVER PHOTO PICTURE

James Haim Pinto (1907-1987), "A Hidden Bay", 1985, acrylic on canvas, 767x765 mm. Courtesy of the International gallery of portrait Tuzla.

INSTRUCTIONS TO AUTHORS

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DTP

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PRINT

SaVart Print, Sarajevo, BA. Printed on acid-free paper.

CIRCULATION

500 copies

THE JOURNAL IS INDEXED IN

Medline/PubMed; EBSCOhost; Index Copernicus; CAB Abstract/Global Health Databases; IndexScholar.com; DOAJ; CrossRef

Acta Medica Academica (ISSN 1840-1848) is an international peer-reviewed biannual journal which is printed as a continuation of the journal Works of the Academy of Sciences and Arts of Bosnia and Herzegovina, Department of Medical Sciences, founded in 1953. *Acta Medica Academica* Online (ISSN 1840-2879) offers free access to all articles at www.ama.ba.

Acta Medica Academica 2014;43(1):1-2
DOI: 10.5644/ama2006-124.93

The Split initiative, chapter 2

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Received: 10 April 2014; Accepted: 19 April 2014

For decades, family medicine was struggling to gain its academic recognition. Now it is safe to say that the success of academic development of family medicine in Europe has been remarkable. Family medicine has been successful in creating its theoretical background and in promoting itself as an academic discipline (1). Throughout Europe, academic departments of family medicine have been established and it is now customary that every student at medical school is taught family medicine as a part of obligatory curriculum (2). Specific training for family medicine is being recognised as a standard for modern patient care. It is accepted in the EU and aspired to by most of the countries that want to join the EU (3).

When a discipline reaches this level of development, international collaboration within the discipline must reflect it as well. Doctors of family medicine no longer meet solely as individuals sharing their experiences in everyday work. They also meet as experts sharing their experiences in education and research. Often they do not do this as individuals, but as representatives of institutions: departments of family medicine and national colleges.

The creation of the Split initiative was a result of such a development. The first meeting in Split marked the first ever organised gathering of family medicine departments from former Yugoslavia. The meeting was a success, not only in getting the departments together, but also in publishing most of the key papers in an international journal (1).

Nevertheless, for an activity to be successful, one successful attempt is not enough. We are therefore proud to present the publication, based on the presentations of the second meeting of the Split initiative. This in itself is a proof of the vitality of the discipline and the quality of the teaching of family medicine in the countries that have participated in this event.

The theme of the first meeting of the Split Initiative (held in Split in 2011) was about modern trends in teaching family medicine in medical schools. Selected articles of this

meeting were published in thematic issue "Contemporary Medical Teaching in Family Medicine" of the journal Acta Medica Academica Vol 41, No 1, 2012 (http://www.ama.ba/index.php/ama/issue/ view/18).

The second meeting (Ljubljana 2013) was on international cooperation in academic family medicine. The selected works (International Textbook of Family Medicine: The application; Satisfaction with the Program of School Bullying Prevention and Mental Health Promotion – Cross Sectional Study among Primary School Pupils in Mostar; Final year medical students' understanding of family medicine; Importance of international networking in academic family medicine; Academic cooperation in family medicine: a viewpoint from Split; Research projects in family medicine funded by the European Union and Fundamental communication skills in medical practice as small elective subject) of the this meeting are presented in this issue of Acta Medica Academica.

We believe that these reports offer to international readers both valuable ideas and inspiration for analysis and initiative on advancement of international cooperation in academic family medicine. There is no reason, rational, professional, or technical why the international collaboration in this medical field would not follow and utilize the paths of cooperation already tested and developed in other medical fields (1, 4). This means that the work should be widened from gatherings (meetings, symposia and congresses) to collaboration in applying to international research grants, exchange of students and scientists, multicentre scientific collaboration and all other models that have been confirmed as efficient in most of other fields of academic medicine. We dare to suggest that, owing to specificities of work in family medicine, like the early contact with patients, direct and early encounter of the disease and orientation towards patients' family and social life, family medicine may develop additional, novel and original models of international collaboration. Our field of work is marked with special needs for patient-centred care, which encompasses extended communication with patients, permanent empathy and understanding, and the first, and thus maybe the most important point of patient-physician shared decision making (5). In this respect, we believe that the Split Initiative will in due time bring about novel and valuable pieces of contribution to various aspects of medical care for people with health problems in the widest sense of the health needs of the contemporary time.

Conflict of interest: The authors declare that they have no conflict of interest.

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Original article

Acta Medica Academica 2014;43(1):3-9
DOI: 10.5644/ama2006-124.94

The sensitivity of male rat reproductive organs to monosodium glutamate

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Received: 24 June 2013
Accepted: 29 November 2013

Objective. This study aimed to investigate the sensitivity of the testis, epididymis, seminal vesicle, and sperm acrosome reaction (AR) to monosodium L- glutamate (MSG) in rats. **Materials and methods**. Rats were divided into four groups and fed with non-acidic MSG at 0.25, 3 or 6 g/kg body weight for 30 days or without MSG. The morphological changes in the reproductive organs were studied. The plasma testosterone level, epididymal sperm concentration, and sperm AR status were assayed. **Results**. Compared to the control, no significant changes were discerned in the morphology and weight of the testes, or the histological structures of epididymis, vas deferens and seminal vesicle. In contrast, significant decreases were detected in the weight of the epididymis, testosterone levels, and sperm concentration of rats treated with 6 g/kg body weight of MSG. The weight loss was evident in the seminal vesicle in MSG-administered rats. Moreover, rats treated with MSG 3 and 6 g/kg exhibited partial testicular damage, characterized by sloughing of spermatogenic cells into the seminiferous tubular lumen, and their plasma testosterone levels were significantly decreased. In the 6 g/kg MSG group, the sperm concentration was significantly decreased compared with the control or two lower dose MSG groups. In AR assays, there was no statistically significant difference between MSG-rats and normal rats. **Conclusion**. Testicular morphological changes, testosterone level, and sperm concentration were sensitive to high doses of MSG while the rate of AR was not affected. Therefore, the consumption of high dose MSG must be avoided because it may cause partial infertility in male.

Key words: Monosodium L- glutamate (MSG), Testis, Testosterone, Sperm acrosome reaction.

Introduction

Monosodium L- glutamate (MSG) is a major flavor enhancer used as a food additive. The concentrations of MSG used as food additive vary in different foods (1). Currently, the safe concentration of MSG in foods and its toxicity in human is still a controversial issue (2). In animals, MSG at higher doses was demonstrated to be a neurotoxic salt that could alter the hypothalamic-pituitary-adrenal axis (HPA) and damage neurons in the hypothalamic nuclei (3-6). In addition, the damages

of liver and kidney could be induced by excessive MSG administration (7). Those findings imply that free glutamate dissociated from MSG may act on their specific receptors in the central neurons or some peripheral cells, resulting in their pathological alterations.

There have recently been several reports indicating that administration of MSG may affect the sperm count in both neonatal and adult animals (8-11) and the glutamate receptors and transporters are expressed in the testis and sperm of mice, rats, and humans (12, 13). However, the roles of glutamate receptors present in male reproductive organs, including the sperm, have not been elucidated. Moreover, no systemic examination of male reproductive organs and of the sperm physiology, such as endogenous sperm capacitation and acrosome reaction MSG-treated rats in various doses, has been performed. Therefore, this study attempted to examine the sensitivity of the entire male reproductive system and the sperm acrosome reaction to varied doses of MSG administration.

Materials and methods

Animals and treatment

Sprague-dawley male rats (8-week-old) were purchased from the Laboratory Animal Unit, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. Thirty-two animals were randomly divided into 4 groups (n=8 for each) and kept in groups of four in cages (60×30×20) with food and water available ad libitum. The control group was treated with distilled water (vehicle) and the treated groups were administered with non-acidic MSG solutions at concentrations of 0.25 (pH 7.3), 3 (pH 7.17), and 6 (pH 7.24) g/kg body weight, daily, by gavages for 30 days. The selected doses were based on the toxicity levels reported by previous authors (14, 15): 0.25 g/kg body weight for non-toxic dose MSG, 3 and 6 g/kg body weight for slightly toxic and highly toxic doses, respectively. The animals received twice a day (between 0 and 8 h) half of the given concentrations of MSG for each feeding period to avoid damage to the rat's stomach from single excess administration of MSG, resulting in unhealthy animals (our preliminary results). This study was approved by the Animal Ethics Committee of Khon Kaen University, based on the Ethics of Animal Experimentation of the National Research Council of Thailand (ref. no. 0514.1.12.2/70).

Morphological study

On the day after the termination of MSG administration, all the animals were euthanized by cervical dislocation and gently sacrificed to collect the male reproductive organs (testes (TE), epididymis (EP), vas deferens (VD), and seminal vesicle (SV). Then, the organs of all groups were observed for gross lesions, recorded in color photography, and were subsequently removed, cleaned of fats, and weighed. Tissues of TE, EP with VD, and SV were extirpated from the right side and they were fixed with 10% formalin in PBS (pH 7.4), and embedded in paraffin, and sectioned at 4-6 μm thick and stained with hematoxylin-eosin (H and E). All images were captured by a Nikon light ECLIPSE E200 microscope equipped with a DXM1200 digital camera.

Plasma testosterone assay

Plasma testosterone concentration was measured by enzymatic immunoassay performed in the facilities of the radiology unit of Srinagarind Hospital, Faculty of Medicine, Khon Kaen University.

Sperm count and acrosome reaction assay

Rat sperms were collected from the left caudal epididymis plus vas deferens and placed into 1 ml phosphate buffered saline (PBS, 37°C, pH 7.4) and further centrifuged (500 xg, 37°C, 5 min.) to separate the sperm

pellet from the epididymal fluid. For epididymal sperm concentration analysis, the sperm pellets were re-suspended with 1 ml potassium-enriched simplex optimized medium (KSOM) and supplemented (Embryo-Max KSOM Powdered Mouse Embryo Culture Medium; Millipore catalogue number: R-MR-020P-5D) with 0.3% bovine serum albumin (BSA). The sperm solutions (1:20 dilution) were counted according to the standard procedure in a Neubauer counting chamber (16). To evaluate the percentage of the endogenous acrosome reaction (AR), a small aliquot of the sperm suspension was subjected to Coomassie blue staining as previously described (16-19).

Statistical analysis

One-way ANOVA and Student's t-test were used to examine the significant differences between two or more sets of data, and between two data points, respectively, using the program of Sigma Stat version 3.1.1. All quantitative results are presented as the mean ± SD.

Results

Morphology and weight of male reproductive organs

In comparison with the control group, no marked differences were found in the size, shape, and surface features of the testes among the groups of rats treated with all doses of MSG (Figure 1a). In contrast, the epididymis plus vas deferens (Figure 1b) and the seminal vesicle (Figure 1c) of rats treated with 6 g/kg MSG were smaller than those of the control, as well as the two rat groups treated with 0.25, and 3 g/kg body weight of MSG (Figures 1b and 1c).

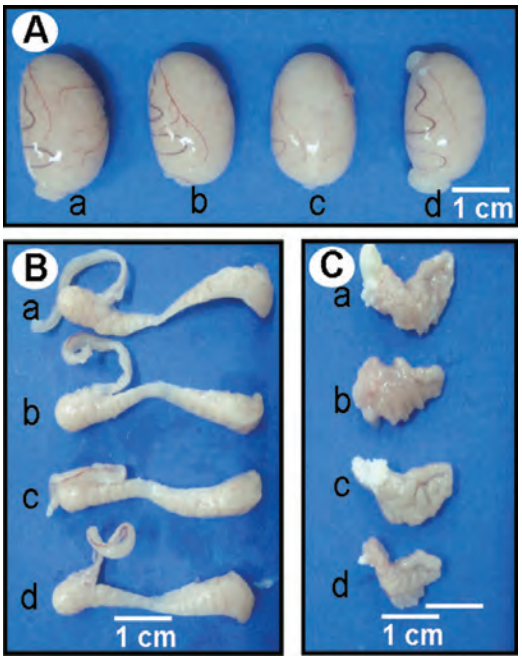

Figure 1 Photographs showing the gross morphology of right testis (A), epididymis and vas deferens (B), and seminal vesicle at right side (C) from control (a) and treated rats with MSG at 0.25 (b), 3 (c) and 6 (d) g/kg body weight.

The weight of the different organs from the different groups was measured (Table 1). No significant differences were found among testes of any groups administered MSG as compared with the control group ($p>0.05$)

Table 1 The effect of monosodium glutamate on testicular, epididymis plus vas deferens, or seminal vesicle weight (g) in rats (mean ± SD, n=8 in each group)

Groups	Weights (g)		
	Testes	Epididymis plus vas deferens	Seminal vesicle
Control	1.6829±0.05	0.5068±0.01	0.8769±0.04
0.25 g SG/kg/BW	1.6812±0.03	0.4803±0.02	0.6836±0.07*
3 g MSG/kg/BW	1.5988±0.06	0.4727±0.01	0.6579±0.06*
6 g MSG/kg/BW	1.5874±0.04	0.4283±0.02*	0.3904±0.08**

BW= body weight; *p<0.05; **p<0.01.

(Figure 1 and Table 1). The weight of the epididymis plus vas deferens was significantly decreased only in the 6 g/kg body weight of MSG group as compared with the control ($p<0.05$), while the weight of the seminal vesicle decreased in all MSG-treated groups with a marked decrease in the 6 g/kg body weight of MSG group ($p<0.01$).

The effect of MSG on testicular histology

No marked changes in histology were noted in the testes of rats receiving 0.25 g/kg body weight of MSG as compared with the control group (Figure 2a and 2b). However, a mild slouching of spermatogenic cells in the seminiferous tubular lumen was observed in approximately 10-15% of the seminiferous tubules obtained from eight animals administered with 3 g/kg body weight of MSG (Figure 2c). Moreover, mild sloughing of such seminiferous tubules with some vacuolization and some shrinkage of the interstitial tissues with wider empty spaces were noticed in approximately 40-45% of rats administered with 6 g/kg body weight of MSG (Figure 2d).

Effect of MSG on plasma testosterone

When compared to the control, the plasma testosterone levels were significantly lowered in 3 g/kg body weight of MSG ($p<0.05$) and of 6 g/kg body weight of MSG ($p<0.01$), whereas the testosterone levels in rats with 0.25 g/kg body weight of MSG were normal ($p>0.05$) (Figure 3).

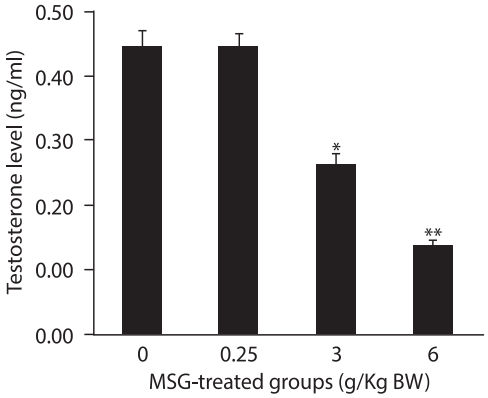

Figure 3 Testosterone plasma levels (ng/ml) determined after treatment in control and MSG treated groups (0.25, 3 and 6 g/kg body weight, respectively). Statistically significant difference from control (*$p<0.05$; **$p<0.01$).

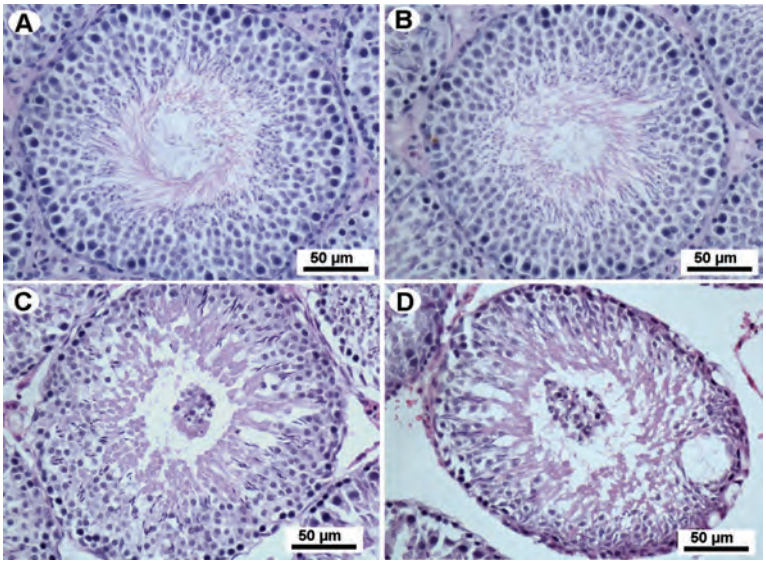

Figure 2 Light microscopy of the seminiferous tubules from rats treated with or without MSG. (A) Control group. (B, C, and D) MSG treated groups (0.25, 3 and 6 g/kg body weight, respectively). Note: slouching of spermatogenic cells in the lumen of seminiferous tubules were observed only in MSG treated groups at 3 (C) and 6 (D) g/kg body weight.

Table 2 The effect of monosodium glutamate on epididymal sperm concentration and acrosome reaction in rats

Groups	n	Effect of monosodium glutamate	
		Epididymal sperm concentration (x 10^6 sperm/ml; mean ± SD)	Acrosome reacted sperm (%)
Control	8	36.88±2.40	4.1
0.25 g MSG/kgBW	8	34.25±4.01	5.7
3 g MSG/kgBW	8	36.93±3.09	6.4
6 g MSG/kgBW	8	24.70±6.02*	4.4

BW= body weight; *p<0.05.

Sensitivity of sperm count to MSG

The epididymal sperm concentration and the percentages of sperms representing the endogenous acrosome reaction are shown in Table 2. The administration of 0.25 and 3 g/kg body weight of MSG did not affect the epididymal sperm concentration when compared with the control group. In contrast, the epididymal sperm concentration was significantly decreased in the 6 g/kg body weight of the MSG group, compared with the control or two lower dose MSG groups. In the acrosome reaction assays, there was no statistically significant difference between the control and three different MSG treated groups (p>0.05).

Discussion

Our morphological findings indicate that the epididymis plus vas deferens and, in particular, the seminal vesicles, but not the testes, are very sensitive to MSG administrations. In accordance with this finding, a previous study showed that the oral administration of 4 g/kg body weight of MSG did not affect the testicular morphology (11).

França et al., (9) reported histological alterations of the testes in prepubertal 4 mg/kg body weight of MSG rats and found a significant reduction of spermatogenic cells (SCs) in the testes of adult MSG rats. Their finding of SCs is supported by our present finding that these SCs were sloughing into seminiferous tubule lumen (Fig 2c and 2d). In a previous study, the expressions and localizations of metabotropic glutamate (mGlu) receptors were demonstrated in both rat and human testicular tissues, particularly in SCs (12). It is possible that excessive glutamate dissociated from exogenously administered MSG rats may hyper-activate the mGlu receptors present in SCs, resulting in an excess of calcium influx, which may induce such testicular pathological changes as sloughing of SCs into the tubular lumen. In contrast to the testes, the epididymis plus vas deferens and the seminal vesicle exhibited no marked changes in histology in all the MSG treated groups, when compared to the control (data not shown).

MSG has been demonstrated to exert neuronal toxic effects in the central nervous system (CNS), including the hypothalamo-pituitary (HP) axis (3, 20-23). The plasma levels of gonadotropic hormones (FSH and LH) and testosterone, and the total number of Leydig cells have been reported to be significantly decreased in prepubertal rats treated with 4 mg/kg body weight of MSG (9). In adult male rats, it has been shown that administration of 4 g/kg body weight of MSG significantly decreased the plasma testosterone level (11). The present reduction in the plasma testosterone levels may therefore be due to the disruption of the HP axis in the MSG treated rats. In addition, it

is possible that the total number of Leydig cells responsible for testosterone production may decrease, as suggested by the marked shrinkage of the testicular interstitial tissues of the MSG groups (Figure 2c and 2d) compared to the control (Figure 2a). The quantitative comparison of the number of Leydig cells among MSG-rats and normal rats remains to be investigated.

The present decreased epididymal sperm concentration in rats treated with a high dose MSG (6 g/kg body weight) is consistent with previous studies (9-11). In addition, our results further demonstrated decreases in the size and weight of the epididymis, some histological changes in the testes, and a depletion of plasma testosterone hormone in rats treated with a high dose of MSG. Since the localization of glutamate receptors and transporters have been reported in animal and human sperms (13), it is possible to expect that free exogenous glutamates dissociated from MSG are released into the epididymal fluid and may enhance the acrosome reaction through the glutamate receptors and transporters. However, no significant difference was found in the rate of the acrosome reacted sperm in all groups (Table 2). One of the possible explanations for this negative finding is that the epididymal sperms were masked with some epididymal molecules in a way similar to that preventing the pre-capacitation or pre-acrosome reaction factors, resulted in the inability of free glutamates to act on their receptors or transporters, allowing the acrosome reaction process.

Conclusion

In conclusion, our study examined histopathological changes in the seminiferous tubules of rats that received various doses of MSG. The decrease of testosterone and epididymal sperm concentration may depend on the level of the MSG dose. Although glutamate receptors and transporters have been localized in the mature sperm, their functions responsible for acrosome reaction are not elucidated. To clarify this function, the percoll gradient-centrifuged (PGC) capacitated sperm (free from masking of the epididymal molecules) may be used, incubated with purified glutamate, to investigate whether glutamate could induce acrosome reaction or not. In this study, we first examined the endogenous sperm acrosome reaction status in MSG-treated rats. The analysis of the amount of free glutamate present in the epididymal fluid of MSG rats and the in vitro acrosome reaction assay by incubation with washed epididymal sperms and pure glutamate need to be further clarified.

Authors' contributions: Conception and design: SI, WH, HK; Acquisition, analysis, and interpretation of data: SI, WS, JY, PK, DF; Drafting the article: SI, WS, HK; Revising it critically for important intellectual content: SI, HK, WS.

Acknowledgements: This project was supported by Invitation Research Grant 2012, Faculty of Medicine (No. I-55102), Khon Kaen University, Thailand.

Conflict of interest: The authors declare that they have no conflict of interest.

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Original article

Acta Medica Academica 2014;43(1):10-18
DOI: 10.5644/ama2006-124.95

Most common HCV genotypes in patients from north-eastern Croatia

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Received: 17 September 2013
Accepted: 13 January 2014

Objective. The aims of this study were to determine the HCV-RNA viral load, genotype distribution, risk factors and symptoms of HCV-RNA positive viral load in HCV antibody-positive patients from north-eastern Croatia. **Materials and methods.** From January 2009 to December 2011, 203 HCV antibody- positive patients (130 men and 73 women; median age 44.5 years) were analyzed for HCV-RNA by the COBAS TaqMan HCV test and genotyped by the Linear Array HCV Genotyping test (both from Roche). All patients completed a structured questionnaire about risk factors and symptoms. **Results.** The HCV-RNA percentage was 61.1% and was similar for men and women. The HCV-RNA viral load increased with age: while 55% of 20-50 year old patients were HCV-RNA positive, 73% of patients >50 years were positive (p=0.021). Genotype 1 was the most prevalent genotype (79.8%), followed by 3 (12.9%), 4 (6.5%), and 2 (0.8%); genotypes 5 and 6 were not determined. Patients with genotype 1 (median, 50 years) were older than patients with 3 (median, 33.5 years) or 4 (median, 38 years). The blood transfusions performed in Croatian hospitals before 1993 was significantly associated with HCV-RNA positive viral load (p<0.05). **Conclusion.** These data indicated an elevated prevalence of genotype 1 in elderly HCV-RNA positive patients and it may continue to rise. Using RNA-based detection in HCV positive-antibody patients would allow early detection of HCV in the acute stage of HCV disease and the increased risk of HCV genotype-related treatment failure.

Key words: HCV-RNA, HCV genotypes, HCV antibody-positive, Risk factors.

Introduction

Hepatitis C virus (HCV) was discovered in 1989 as the main cause of 90% of cases of after-transfusion hepatitis, previously known as 'non-A, non-B hepatitis'. According to the World Health Organization (WHO), HCV infection is a global health problem. It is estimated that 7.3–8.8 million people in Europe are infected with HCV (1.1–1.3% of general population), leading to 86,000 deaths and 1.2 million of hospitalizations (1). Two hundred cases of acute and a similar number of chronic infections with hepatitis C virus (HCV) are registered in Croatia every year. With an estimated 1.3% of HCV-positive persons in the general population, Croa-

tia is one of the countries with a low HCV prevalence. Despite the legislation from 1992, which obliges all general practitioners to report infectious diseases to the Institute of Public Health (2), HCV screening and its epidemiological treatment have still not been regulated. For instance, a 2006 study from Zagreb reported that 78% of family members of infected individuals were not being monitored nor informed about HCV transmission risks (2). Moreover, high-risk individuals are not routinely surveyed for acute HCV infection.

Legislation has not included the regulation of epidemiological treatment of HCV infected individuals or their screening and informing them about all known HCV transmission risks, such as sexual intercourse, needle sharing among injection drug users etc. (3). It is not obligatory for Epidemiology Departments to monitor HCV-positive patients, but they do it through patient healthcare and contact tracing. After a certain period they test the sexual partners of the patient or those that are at greater risk of infection.

Contaminated blood is the main route for HCV transmission. Since the introduction of the obligatory testing of voluntary blood donors for anti-HCV antibodies in 1993, the spread of HCV through transfusions and hemodialysis has been almost completely eliminated in Croatia. However, intravenous drugs, sharing injection needles and tools for tattoos and body-piercing are today the most common modes of HCV transmission. Sexual transmission, organ transplantation, and invasive diagnostic and therapeutic approaches are additional risk factors for HCV infection. In fact, each hospitalization, even without transfusion, is a risk factor for HCV infection (4).

The currently used strategy for combating HCV infection in Croatia is a combined therapy with pegylated-interferon and ribavirin (PEG-INF/RBV). It is offered to individuals with two successively increased alanine aminotransferase (ALT) levels, stage F2 liver fibrosis (according to Ishak), co-infection with hepatitis B virus (HBV), human immunodeficiency virus (HIV) or HCV genotypes 2 or 3, liver transplantation, and/or severe extra-hepatic symptoms. The success of this approach is however low in patients infected with the HCV genotype 1, who respond inefficiently to therapy with PEG-INF/RBV and suffer from many adverse side effects (5). Moreover, due to the lack of routine screening of the high-risk population in our country, treatment of HCV infections begins at the chronic phase, which is more refractory to therapy and associated with an increased incidence of blood disorders, autoimmune disorders, skin conditions, and kidney disease (6). Finally, many chronic patients have normal levels of liver enzymes and do not receive therapy.

North-east Croatia has a higher mortality rate from chronic HCV infections than the rest of the country. Chronic infection-related death is the 15th cause of death nationwide but the 10th cause in our county (7, 8). The reason for this remains elusive due to the limited data about HCV epidemiology in this region.

Therefore the aim of this study was to assess the genotype distribution, transmission risk factors, and symptoms of HCV infection in 203 HCV antibody-positive individuals from several cities of the Osijek-Baranja County. Our results suggest that early detection of HCV-RNA in the acute stage of the disease and genotyping of HCV-RNA positive patients could offer more efficient therapies.

Materials and methods

Study Population

Between January 2009 and December 2011, we analyzed the plasma samples of 203 HCV

antibody-positive patients from north-eastern Croatia for HCV-RNA viral load (70.8% of patients were from Osijek, 9.5% were from Beli Manastir, 7.1% were from Našice, 6.9% were from Đakovo, 4.7% were from Donji Miholjac, and 0.5% each were from Valpovo and Belišće), who were referred to our department by general practitioners or family doctors. Of 203 participants, 130 (63%) were men and 73 (36%) women. Their median age was 44.5 years (ages 22 to 82). All participants were informed about the protocol and study objective. Those who gave informed consent were interviewed by a structured questionnaire covering history of hemodialysis, surgical procedures, use of intravenous drugs, tattooing, unprotected sex, and suspected HCV symptoms, such as muscle pain and appetite loss.

Blood Collection

Blood samples were collected at the outpatient clinic of the Institute of Public Health of the Osijek-Baranja County. The blood was collected in 8.5 ml PPT test-tubes (BD Plasma Preparation Tube, Becton Dickinson, Germany) containing a gel for plasma separation, and centrifuged for 10 min at 2,500 rpm/min (Hettich Rotanta 460 R, Germany) not later than 2 hours after collection. Blood samples were stored at –20°C in a vertical position.

Quantitative detection and genotyping of HCV

RNA was isolated from blood samples using the High Pure System Viral Nucleic Acid Kit (Roche Diagnostics, Mannheim, Germany) and quantified by the quantitative COBAS® TaqMan® HCV Test, v2.0 (Roche Diagnostics, Mannheim, Germany) using the COBAS TaqMan 48 instrument. The lower detection limit for HCV-RNA was 25 IU/ml. The HCV-positive plasma samples were further genotyped using the Amplicor HCV Specimen Preparation Kit, v 2.0 (Roche Diagnostics, Mannheim, Germany) and Linear Array Hepatitis C Virus Genotyping Test (Roche Diagnostics, Mannheim, Germany). All assays were performed according to the manufacturer's instructions.

Statistical analysis

The χ^2 and Fisher's exact test, as appropriate, were used to compare percentage data (*i.e.*, distribution of each risk factor between HCV-RNA positive and HCV-RNA negative patients). The Kruskal-Wallis test was used to compare continuous variables (*i.e.*, the mean age between genotypes 1, 2, 3, and 4). Post-hoc analysis was performed by pairwise comparison of subgroups. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to show the strength and direction of associations. For all tests, p values <0.05 were considered statistically significant. Statistical analyses were performed using MedCalc (MedCalc Software version 10.2) and SAS.

Ethical statement

This study was approved by the Ethics Committee of the Institute of Public Health of Osijek-Baranja County (1346/09) and performed according to the ethical principles of the Helsinki declarations.

Results

HCV-RNA distribution by age and sex

HCV-RNA viral load was found in 124 (61.1%) of 203 HCV antibody-positive patients. Table 1 shows that the HCV-RNA viral load was found to be significantly higher (χ^2, p=0.021) in patients older than 50 years (71.8%) compared to 21–50 year old HCV-RNA positive patients (55.3%). As shown in

Table 1 Age and sex related distribution in HCV-RNA positive and negative patients

Age and sex	HCV-RNA		OR (95 %CI)*	p value
	HCV-RNA positive	HCV-RNA negative		
	n (%)	n (%)		
Age (years)				
21-50	73 (55.3)	59 (44.7)	1.00**	0.021
>50	51 (71.8)	20 (27.2)	2.06 (1.11; 3.83)	
Sex				
Female	43 (58.9)	30 (41.1)	1.00**	0.6332
Male	81 (62.3)	49 (37.7)	1.15 (0.64; 2.07)	

*OR= odds ratio; CI=confidence interval; **Reference.

Table 1, there was no significant difference in the HCV-RNA positivity between women (58.9%) and men (62.3%).

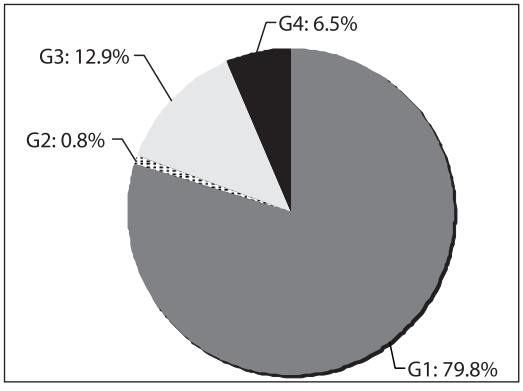
HCV genotype distribution

Genotype 1 was the most prevalent (79.8%), followed by 3 and 4 (12.9 and 6.5%, respectively). Genotype 2 was the rarest genotype as it was detected in only one, 63-year old patient. Genotypes 5 and 6 were not detected (Figure 1).

While there was no significant gender-related variation in the distribution of HCV genotypes, their age-related distribution differed (Figure 2).

We found a statistically significant difference between the distribution of genotypes between the five age groups (Kruskal-Wallis ANOVA, p=0.0055), with a mean rank of 67.81 for genotype 1, 112 for 2, 35.16 for 3, and 45.25 for 4. Post hoc analysis showed that the age-related distribution of genotype 3 infection significantly differed from 1 and 2 ($p<0.05$).

Figure 3 shows that the patients infected with genotype 1 have a higher tendency to be older (median age, 50 years) than those infected with 3 (median, 33.5 years) or 4 (median, 38 years). However, these differences in median age were not significant (Kruskal-Wallis, p=0.3679).



G=genotype.
Figure 1 Overall HCV genotype distribution.

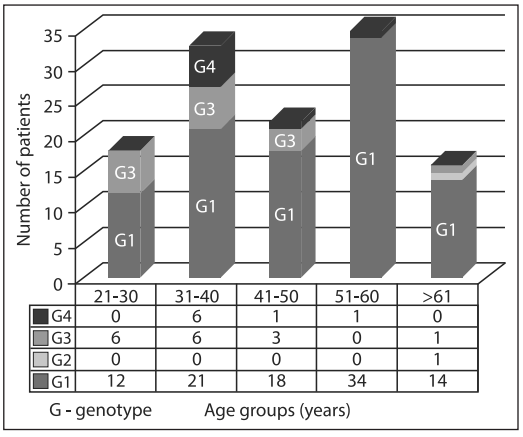


Figure 2 Age-specific distribution of HCV genotypes. The age-related difference between the genotype 1, 3, and 4 distributions was statistically significant (p=0.0055 by Kruskal-Wallis ANOVA).

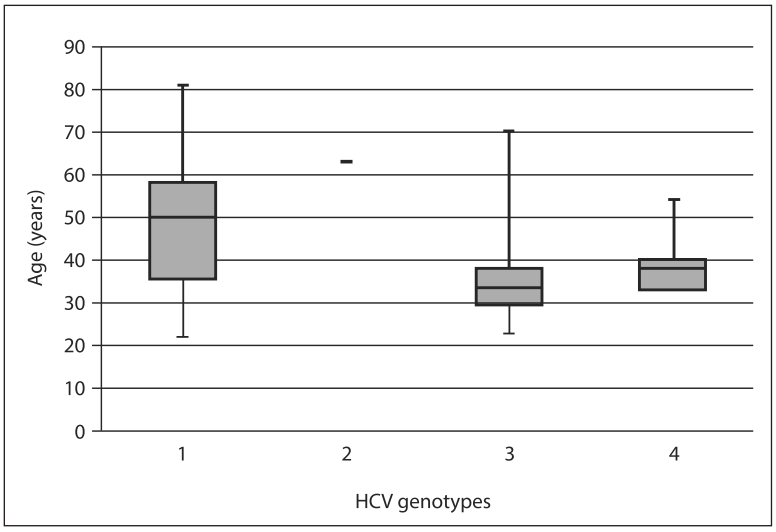


Figure 3 HCV genotype distribution by patient age.

Risk factors and symptoms

Table 2 summarizes the potential risk factors and HCV genotypes that were analyzed here. Univariate analysis showed that the independent predictor of HCV infection by genotype 1 in relation to infection by geno-

Table 2 Comparison of risk factors and HCV genotypes in 124 HCV-RNA positive patients

Risk factors	HCV genotypes				p value*
	1	2	3	4	
	n (%)	n (%)	n (%)	n (%)	
Surgery before 1993					
Yes (n=63)	53 (42.7)	1 (0.8)	6 (4.8)	3 (2.4)	NS
No (n=61)	46 (37.1)	0 (0)	10 (8.1)	5 (4.1)	
Blood transfusion before 1993					
Yes (n=48)	44 (35.5)	1 (0.8)	3 (2.4)	0 (0)	0.010
No (n=76)	55 (44.3)	0 (0)	13 (10.5)	8 (6.5)	
Use of injection drugs					
Yes (n=35)	24 (19.3)	0 (0)	8 (6.5)	3 (2.4)	NS
No (n=89)	75 (60.4)	1 (0.8)	8 (6.5)	5 (4.1)	
Tattoo					
Yes (n=50)	37 (29.8)	0 (0)	10 (8.1)	3 (2.4)	NS
No (n=74)	62 (50.0)	1 (0.8)	6 (4.8)	5 (4.1)	
Muscle pain					
Yes (n=66)	55 (44.3)	1 (0.8)	8 (6.5)	2 (1.6)	NS
No (n=58)	44 (35.5)	0 (0)	8 (6.5)	6 (4.8)	
Appetite loss					
Yes (n=58)	44 (35.5)	1 (0.8)	10 (8.1)	3 (2.4)	NS
No (n=66)	55 (44.3)	0 (0)	6 (4.8)	5 (4.1)	
All patients	99 (79.8)	1 (0.8)	16 (12.9)	8 (6.5)	

*Fisher's exact test; NS=Not statistically significant.

types 2, 3 and 4 was a history of blood transfusion (p=0.010) if performed before 1993. Other risk factors, including surgery before 1993, blood transfusion before 1993, drug use, tattoo, and two symptoms (muscle pain and appetite loss), did not significantly correlate with certain HCV genotype infection.

Discussion

Comprehensive epidemiological data on hepatitis C infection in HCV antibody-positive patients from north-eastern Croatia is limited. Only one study has so far analyzed the distribution of HCV genotypes in 111 infected patients from this region (9). The aim of our work was thus to assess the HCV genotype distribution for tailoring therapeutic modalities.

The HCV-RNA percentage in HCV antibody-positive patients in our community was 61.1% (124/203). Similar disparities in ratio between HCV antibody-positive and HCV-RNA viral load detectable plasma levels have been reported by others (10, 11).

Another important finding of this study is that older patients (>50 years) suffered significantly more from HCV-RNA viral load than younger (<50) ones, which is dissimilar to studies conducted in Brazil and the USA (10, 12). The reasons for this could be mainly because older patients had a greater probability of undergoing blood transfusions and surgery before 1993.

The distribution of HCV genotypes in north-eastern Croatia was similar to other European countries: genotype 1 was the most common type (79.8%), followed by 3 (12.9%), 4 (6.5%) and 2 (0.8%). Genotype 1 prevalence in our region was thus lower than in Romania (97.7%), Hungary (94.5%), Bulgaria (80.8%) but higher than in Slovenia (79%), Germany (70%), Belgium (60%), Serbia (57.6%), Italy (57%), and the Netherlands (49.3%) (13-15). Genotype 1 was the most prevalent genotype in this study, similar to that in HCV-RNA positive patients from other European countries and worldwide (16, 17). Compared to our region, the lower prevalence of genotype 1 in HCV-RNA positive patients from western Europe may be due to earlier diagnosis of HCV infection.

The genotype 3 prevalence in HCV-RNA positive patients in Croatia appeared to be region-specific. While we found that its prevalence in north-eastern Croatia was relatively low (12.9%), genotype 3 prevalence in western Croatia was much higher (43.7%) (9). As the latter study included high-risk subjects residing in Split, a second-largest Croatian city with a large number of drug addicts, this may explain the difference between their and our results. Compared to other countries, the prevalence of genotype 3 in our study was higher than in Italy (5.9%) but lower than in India (63%) (17), Luxemburg (33%), the Netherlands (29%), Germany (26%) (13, 18) and Serbia (21.2%) (15).

The prevalence of genotype 4 infection in HCV-RNA positive patients of north-eastern Croatia was low (6.5%), similar to that in Serbia and Hungary (5% each) but lower than in Belgium (15%) and the Netherlands (11%) (13-15). The higher genotype 4 prevalence in western Europe than in our region may be explained by the fact that genotype 4 has spread from central Africa and the Middle East to Europe by population migration (16, 19-20). Finally, the rarest HCV type in our community was genotype 2. Its prevalence (0.8%) was much lower than in other European countries: Italy 52.4% (21), the Netherlands 10% (18), Belgium 5% (13), Slovenia 5.2% (22), and India 5.6% (17). More studies with a higher number of HCV antibody-positive participants are necessary to confirm the rarity of genotype 2 infection in our community and to verify its putative correlation with increased age.

Another interesting finding of this study was that genotype 1 infections were more

common in older patients, which is very similar to the findings in HCV infected patients in Vienna and the surrounding areas (23), due to two reasons: patients with genotypes 2 and 3 infection are more responsive to the standard combination of PEG-INF/RBV therapy compared to genotype 1 infection, and the most HCV infections through blood transfusion are caused by 1 (14, 18, 23). Carrion et al. (24) found that the prevalence rate of genotype 1 increased with age amongst the European population. In contrast, genotype 3 and 4 HCV infections were common in younger patients. This could be caused by several factors: firstly, the higher level of risky behavior of genotype 3-infected patients. They were significantly more frequently injection drug users than those infected with genotype 1 (50 vs. 24%, respectively, p=0.0374). A similar correlation between intravenous drug use and genotype 3 infections was reported previously. Secondly, genotype 4 infections spread by migration, which may explain why these infections were more common in younger patients (25-27). Thirdly, genotype 1 infections are more refractory to PEG-INF/RBV (23) and may thus remain detectable in older HCV infected patients.

Blood transfusion, intravenous drug use, tattooing, and body-piercing have been the main routes of HCV transmission (28). We found blood transfusion before 1993 as a risk factor significantly associated with HCV infection. This is not surprising since the obligatory analysis of donated blood for anti-HCV antibodies in Croatia began in 1993. Similar findings were reported in Central Africa (29), Brazil (10) and Jordan (30). Unexpectedly, however, factors such as intravenous drug usage and tattooing did not significantly associate with HCV infection in north-eastern Croatia, contrary to data from other studies (31-33). Whether this is due to the small number of participants in our study remains to be elucidated.

Conclusion

In conclusion, despite some limitations (the low number of participants and missing epidemiological evidence about their age at the time of infection and administered therapy), this study was the first to indicate that the majority of HCV-RNA positive patients in north-eastern Croatia were infected with genotype 1. Moreover, it demonstrated that the prevalence of genotype 1 was more pronounced in individuals older than 50 than in other Croatian regions. Due to the aging trend of our community, we might experience a rise in the incidence of genotype 1 infections, especially in individuals with a history of transfusion before 1993. Due to the refractory nature of genotype 1 infection to the PEG-INF/RBV, the financial burden related to its medical treatment might thus surpass the current 19,000 Euro/year (Clinical Health Center Osijek). Routine HCV-RNA-based screenings of high-risk individuals (such as injection drug users, young people with numerous tattoos and/or body-piercing, dialyzed or immunosuppressed patients) would help in the earlier detection of acute stage HCV infections in our community. In addition, HCV genotyping and more efficient therapies for genotype 1 infections, i.e. with protease inhibitors and PEG-INF/RBV therapy (34, 35), would help in diminishing the HCV-related medical costs.

Acknowledgments: The authors would like to thank all participants in our study. The authors also greatly appreciate the help received from Dr Marcela Čović for data analysis and article revision.

Authors' contributions: Conception and design: MP, ZB, DV; Acquisition, analysis and interpretation of data: BŠ, SDž; Drafting the article: NR, IRK; Revising it critically for important intellectual content: VB, JB.

Conflict of interest: The authors declare that they have no conflict of interest.

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Original article

Acta Medica Academica 2014;43(1):19-29
DOI: 10.5644/ama2006-124.96

Immune responses following McKenzie lumbar spine exercise in individuals with acute low back pain: A preliminary study

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Received: 20 November 2012
Accepted: 8 October 2013

Objective. This study explores the immune responses following 4 weeks of McKenzie lumbar spine exercise in individuals with acute low back pain (ALBP). **Patients and methods**. Fifteen patients with ALBP and 15 healthy individuals volunteered in this study. Ten ml of peripheral blood were obtained from each patient before and after exercise sessions, and from healthy individuals at the beginning of the study. Flow cytometric analysis was used to evaluate the frequencies of CD4+ T lymphocyte sub-populations and the intracellular cytokine expression within this cell population. Pain perceptions were obtained at baseline and following each week of exercise sessions. **Results**. In comparison with healthy subjects there was an elevated frequency of memory (CD4+CD45RO+) T cells, helper inducer (CD4+CD29+) T cells, CD3+CD16+CD56+ T cells and a lower frequency of naïve/suppressor (CD4+CD45RA+) T cells at base line in back pain patients ($p<0.05$). After 4 weeks of McKenzie exercise sessions, pain intensity significantly decreased ($p<0.05$); however, there was no significant difference in the frequency of memory (CD4+CD45RO+) T cells, helper inducer (CD4+CD29+) T cells, CD3+CD16+CD56+ T cells and naïve/suppressor (CD4+CD45RA+) T cells at base line relative to these cell populations after exercise sessions. The percentage of Pan (CD3+) T cells expressing IL-8 and TNF-α and the CD3+ T cells expressing the anti-inflammatory cytokine IL-4 increased significantly ($p<0.05$) following exercise sessions in comparison with baseline and healthy references. The reduction in pain scores did not correlate with elevated anti-inflammatory cytokines. **Conclusion**. McKenzie exercise sessions induced an immune activation state and simultaneously up regulated anti-inflammatory IL-4 cytokines that boost pain relief.

Key words: McKenzie lumbar spine exercise, Inflammation, Lymphocytes, Intracellular cytokines.

Introduction

Herniation of an intervertebral disc is implicated in 40% of acute low back pain (ALBP) (1). Mechanical pressure created by the escaped nucleus pulpous, and the inflammatory responses that follow, excite the nociceptive system, and trigger spinal pain and dysfunction (2-4). McKenzie exercises are commonly used to relief pain and restore spine mobility (3, 5-9).

During the McKenzie assessment protocol, the therapist usually observes changes in pain intensity and location, known as the pain centralization phenomenon (3, 5,

6). Centralization of pain, observed only in discogenic pain, and is clinically defined as a shift in the pain from a distal to a more proximal location to the spine, in response to spinal loading by directional preference exercise or positions (3, 5, 6). The physical therapist then prescribes exercises that are performed in the direction that centralizes and/or abolishes the pain (3, 5, 6, 9-11). The positional change of the nucleus pulposus in response to these directional preference exercises is referred to as the dynamic disc model (3, 9). Conceptually, the disc dynamic model proposes that in a healthy disc with intact annulus fibers and hydrostatic mechanisms, the nucleus pulposus will move in the opposite direction to the spinal loading imposed by a specific body position or movements performed in a specific direction (3, 5-9, 12).

Accordingly, pain centralization and the associated pain relief have been exclusively explained on the basis of the disc dynamic model. However, biochemically pain arises from inflammation and inflammatory responses, regardless of its type or nature (1, 2). Biochemical mediators of pain include: cytokines, growth factors, neuropeptides and neurotransmitters (1, 2). The human intervertebral disc is avascular in nature, and the nucleus pulpous is immune-privileged. When a disc is herniated, the escaped nucleus pulpous is exposed to the immune system and triggers the release of pro-inflammatory cytokines, such as: interleukins, (IL)-1, IL-6, IL-8, prostaglandin E2, nitric oxide (1, 2 13-16) and IL-17 (17), as well as other regulatory cytokines including tumor necrosis factor alpha (TNFα), interferon gamma (IFN-γ) and IL-1β. Normally, pro-inflammatory cytokines are counter-balanced by the release of anti-inflammatory cytokines, such as IL-1 receptor antagonist (IL-1rα), IL-10, IL-4, IL-13, and transforming growth factor-ß-1 (TGF-ß1) (1, 13), which maintain homeostasis (1, 13, 18).

There is evidence to suggest that exercise regulates immune responses (19-22). Studies show that changes in the plasma concentration of cytokines depends on the type, intensity, and duration of physical exercise (18, 23-29). Moderately intense exercise boosts the immune system and reduces the risk of infection (27, 30-32), whereas intense and prolonged exercise induces pro-inflammatory cytokines and upper respiratory tract infections (28, 33).

Clinically suppressing pro-inflammatory cytokines by anti-inflammatory agents is usually considered the first-line treatment for patients with ALBP. In physical therapy, a non-invasive, non-chemical modality, such as therapeutic exercise, has been proven to be effective for pain relief. Whether therapeutic spinal exercise sessions trigger immune responses is worthy of investigation. We hypothesize that McKenzie exercises may have an immunoregulatory role that would rationalize pain relief.

Therefore, the aim of this study was to explore the immune responses following 4 weeks of intervention using McKenzie lumbar spine exercises in individuals with acute low back pain.

Methods

Patients

Initially, 65 patients (of Middle Eastern origin) with acute low back pain agreed to volunteer for the study. However, 21 were excluded because they were taking anti-inflammatory medications, 8 did not want to be treated only with McKenzie exercises, 6 did not return after the first visit, even though they demonstrated pain centralization, 15 patients did not demonstrate pain centralization (7 underwent lumbar microdiscectomy, and 8 received epidural injections). The final sample comprised of 15 patients who demonstrated pain centralization (9 males and 6 females; average age, 42.1±2.7 years). The blood of fifteen healthy individuals (8 males and 7 females; average age, 38.5±3.1 years) matched the basis of age, height and weight were used as refer-

ences for normal lymphocyte subpopulations and cytokines expression.

On their first visit to the physical therapy clinic each participant was screened for eligibility for participation in the study. Inclusion criteria were: ALBP lasting between 1 to < 7 days, extending between the 12th rib to the buttock with or without leg pain; with an established diagnosis of disc prolapse; referral for physiotherapy; acceptance to be treated by McKenzie exercises only, and not receiving worker's compensation. Exclusion criteria were: a spinal inflammatory and infectious disease; spinal fracture or dislocation; motor or sensory deficit; surgery within the past 6 months; concurrent inflammatory conditions; pregnancy; cardiopulmonary diseases; diabetes; cigarette smokers, utilization of pain medication (nonsteroidal anti-inflammatories drugs, steroids and analgesics), and psychotropic medications. Written consent was obtained from each participant and the study was approved by the institutional ethical committee.

Measurement of pain perception

Pain perception was measured by the visual analog scale (VAS), which is a 100-mm line used to reflect patient responses regarding pain intensity. The anchor terms on the VAS for overall pain and actual reported pain were: 0 mm for "no pain" and 100 mm for "maximum pain imaginable". Two types of pain perception were measured using two separate sheets of VAS; Overall pain (OP) measures pain throughout the day, and actual pain (AP) measures the intensity of pain at the time of the visit. High test–retest reliability has been found for the VAS, as well as high reliability when measuring multiple dimensions of pain, such as intensity, distress, and pain anticipation (34, 35). Pain measurements were obtained at the initial visit, prior to the McKenzie assessment, and at the end of each week.

Mackenzie assessment procedure

The McKenzie assessment protocol uses standardized questions soliciting information related to demographics, pain intensity, posture, nature of pain and general health. The objective information include: physical examination of posture, screening for spinal deformity, lumbar spine range of movement, and repeated spinal movement testing in a specific direction; in lying and standing postures with reference to pain and symptoms. Repeated spinal movements are: lumbar extension and flexion in standing and lying positions, lumbar side gliding when standing, and assessment of static end-range positions. Any change in the location of the pain was documented to determine occurrence of pain centralization. The procedure was repeated within 24–48 hours to confirm pain centralization (3, 5, 6, and 11). Pain centralization was based on the operational definition given by Werneke et al. (5, 6), and changes in pain location on body diagrams.

Treatment

Treatments were individually designed following the Robin McKenzie treatment techniques (3). The treatments included: use of sustained end-range positions, repeated directional preference exercises, vertebral mobilizations, and the use of passive lumbar supports. Exercises and manual techniques were implemented according to the McKenzie objective lumbar spine examinations. Movement(s) associated with pain centralization determined the direction of exercise, while movement(s) associated with peripheralization were avoided (3, 5, 9). Home exercises were selected from the directional preference exercises that enhance pain centralization and each patient was instructed to repeat the prescribed home exercises every 2 hours. Standardized instructions and advice regarding posture correction and the

use of passive lumbar supports were given to all participants (3). Treatment visits were scheduled within 24–48 hours of the initial assessment, with a minimum of 2 visits per week and a maximum of seven sessions over 4 weeks. Werneke et al. (5, 6) concluded that further reductions in lumbar pain are not to be expected if favorable changes in pain location are not evident by the 7th visit.

Satisfaction with treatment was based on the McKenzie criteria of recovery that included: reduction or total abolition of pain, recovery of full spinal movement previously avoided, and the ability to maintain good posture (3). In this study reduction in VAS >50% of base line scores of both the actual and the overall pain was considered satisfactory. In one study reduction of VAS of low back pain, correlated with reliable scales of the Short-Form 36 (SF-36), in particular the body-related dimension ($r=0.52$ and 0.70, $p<0.001$) (35). No restrictions were placed on healthy individuals in terms of routine daily activities, sports or diet.

Phlebotomy and analysis of lymphocyte subpopulations

On the initial visit, and prior to McKenzie assessment and treatment, a 10 ml of venous blood was drawn from the right arm of each participant. Blood was drawn into tubes containing EDTA and the different lymphocyte subpopulations analyzed. In brief, 50 µl of blood was added to 5 µl of fluorescein-isothiocyanate (FITC) or phycoerythrin (RD1)-conjugated monoclonal antibodies against the surface markers of interest, and incubated for 30 min at room temperature. Blood cells were then treated with Q-prep (Coulter Corporation, Hialeah, FL, USA). A two-color fluorescence analysis was performed using an automated flow cytometer (Coulter FC 500). Monoclonal antibodies (Coulter Corporation, Hialeah, FL, USA), specific for human T-lymphocytes (CD3, CD4), natural killer (NK) T cells (CD16/CD56) and indicators of lymphocyte activation (CD29, CD45RA, CD45RO) were used in the study. The blood was collected from all patients at baseline and immediately following 4 weeks of McKenzie exercise sessions. The participants in the healthy group donated 10 ml of blood at the beginning of the study, which was used as a reference for normal lymphocyte subpopulations and cytokine expression.

Cell cultures and intracellular cytokine analysis

Peripheral blood mononuclear cells (PBMC) were separated by Ficoll-Paque (Pharmacia, Uppsala, Sweden) density gradient centrifugation. Cells were washed and suspended in RPMI 1640 medium (Gibco BRL, Gaithersburg, MD) at density of 1×10^6 cells/ml. PBMC were cultured in 96-well plates (200 µl/well) and incubated for 24 hours at 37 °C. The cells were stimulated with 50 ng/ml of phorbol 12-myristate 13-acetate (PMA) 1mg/ml of ionomycin) and 2 mM monensin (Sigma, St. Louis, MO), and intracellular cytokine levels (IL1-β, IL-6, IL-8, TNF-α, IFN-γ, IL-4 and IL-13) were assessed by flow cytometry after three-color immunofluorescence staining.

Statistical analysis

Mean and standard deviation were reported for all variables. The Wilcoxon signed ranks test was used to compare differences between lymphocyte subpopulation frequencies in peripheral blood, cytokine expression of stimulated cells, and pain intensities at baseline and following every week of McKenzie intervention. For all variables, the patients were compared with the reference levels using the Kruskal-Wallis test, and if significant, the Mann–Whitney U-test was applied. Spearman rank correlation was

used to correlate between pain scores and lymphocyte subpopulations and cytokines levels before or after intervention. Data were analyzed using the Statistical Package for Social Sciences version 17 (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

Table 1 shows the demographic data for the ALBP patients. Table 2 displays a significant reduction in both pain scores after 4 weeks of McKenzie exercise sessions, more after the 4th week of intervention relative to the baseline ($p<0.01$).

Figure 1 displays the flow cytometric analysis of the blood samples, show-

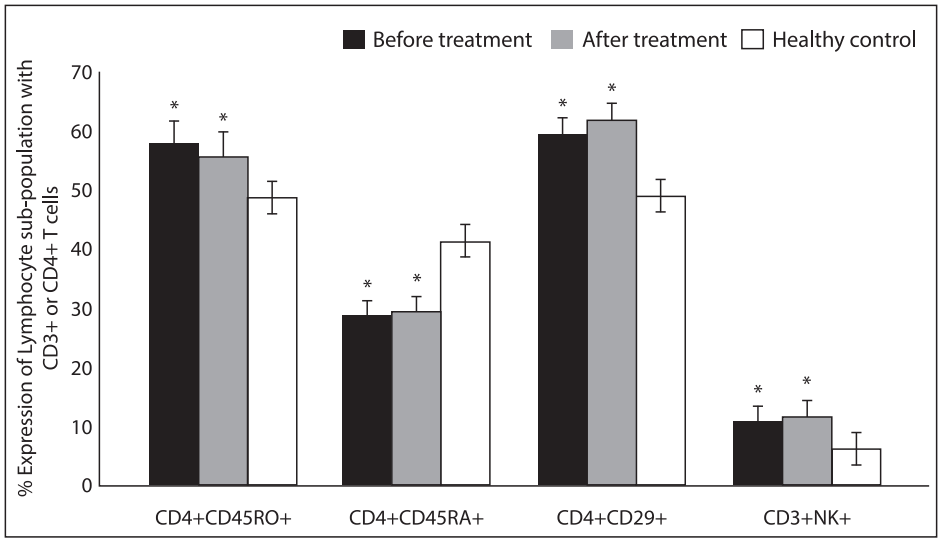
Table 1 Demographic data of patients with acute low back pain

Demographic data	$\bar{x}$±SD
Age (years)	42.0±7.9
Height (cm)	172.9±3.8
Weight (kg)	69.3±5.2
Body mass index (kg/m^2)	23.2±2.1
Pain duration (months)	4.6±1.4

Table 2 Measurements of pain at baseline and following McKenzie interventions

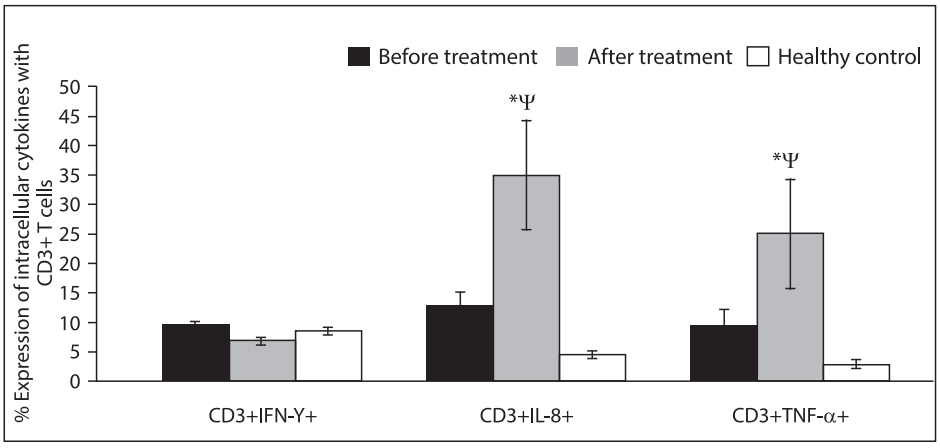
Pain characteristics	Baseline	Week 2	Week3	Week4
Overall pain ($\bar{x}$±SD; Range) mm	88.8±0.87; 78-94	72.1±2.6*; 62-86	58.2±2.3*; 48-70	38.8±2.6**; 20-49
Actual reported pain ($\bar{x}$±SD; Range) mm	89.0±2.1; 79-98	52.9±4.4*; 41-79	26.6±2.7*;11-42	6.9±3.0**; 10-32

*Compared to baseline ($p<0.05$); **Compared to baseline ($p<0.01$).



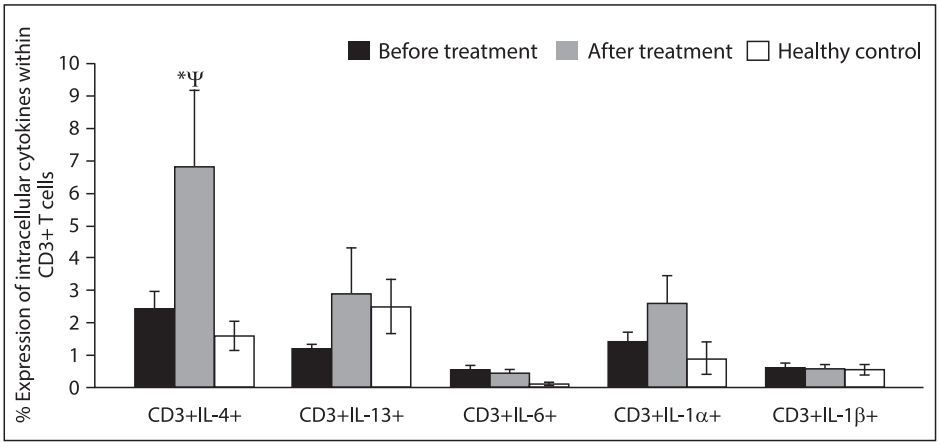
Mean ± SE of % expression of lymphocyte subpopulations within CD3+ or CD4+T cells. No significant change in expression of lymphocyte subpopulations was observed after McKenzie exercises relative to baseline. *$p<0.05$ versus healthy references.

Figure 1 Lymphocyte sub-populations before and after 4 weeks of McKenzie exercises in patients with acute low back pain.



Mean ± SD of % expression of intracellular cytokines within CD3+ T cells. McKenzie exercise induced a significant increase in CD3+IL-8+ and CD3+TNF-α+ T cells.*p<0.05 versus before treatment, Ψp<0.05 versus healthy references.

Figure 2 Intracellular cytokine expression before and after 4 weeks of McKenzie exercises in patients with acute low back pain.



Mean ± SD of % expression of intracellular cytokines within CD3+ T cells. McKenzie exercises induced a significant increase in CD3+IL-8+ and CD3+TNF-α+ T cells.*p<0.05 versus before treatment, Ψp<0.05 versus healthy references.

Figure 3 Intracellular cytokine expression before and after 4 weeks of Mckeinze exercises in patients with acute low back pain.

ing no significant differences in the frequency of memory (CD4+CD45RO+) T cells, helper inducer (CD4+CD29+) T cells, CD3+CD16+CD56+ T cells and Naive (CD4+CD45RA+) T cells after 4 weeks of McKenzie exercises relative to the baseline. The percentage representation of Pan (CD3+) T cells expressing the inflammatory cytokines IL-8 and TNF-α and the CD3+ T cells expressing the anti-inflammatory cytokine IL-4 increased significantly ($p<0.05$) following exercise relative to the baseline and healthy subjects (Figure 2 and 3). The percentage expression of CD3+IL-13+ T cells were increased, but not to a significant level (Figure 3). No correlation was found between pain scores (OP and AP) and lymphocyte subpopulations or the percentage expression of cytokines within CD3+ T cells.

Discussion

The effectiveness of McKenzie directional preference exercises for ALBP has been reported by several studies.(4, 6-8, 10). The pain centralization phenomenon that occurs when performing the directional preference exercises has been reported to decrease or abolish the pain and associated symptoms, increase spinal range of motion, leading to fast recovery, and return to work, whereas delayed recovery, chronic pain and poor outcomes are associated with absence of pain centralization.(4, 6-8, 10).

McKenzie exercises did not induce expansion in the cell surface activation markers; our preliminary results showed no significant change in the frequencies of CD4+CD45RO+ T cells, CD4+CD29+ T cells, CD3+NK+ T cells and CD4+CD45RA+ T cells in the blood samples from our ALBP patients after McKenzie exercises, relative to the baseline (Figure 1). These cell species are major mediators of inflammation.

There is evidence that the CD4+CD29+ T cells (a helper/inducer subset) increase in the peripheral blood of patients with a T-cell mediated disease, such as Guillain–Barre syndrome (36), and T cells with NK surface markers express humoral factors that regulate inflammatory responses in a wide range of immune conditions, including: infections, anti-tumor responses, allograft rejection, graft-versus-host disease (37-39), and autoimmunity (40-42). However, the increased level of these activated lymphocyte subsets at baseline and following intervention observed in the present study may be due to the ongoing inflammatory status caused by the deranged intervertebral disc.

McKenzie lumbar spine exercises are considered to be of light intensity (43, 44) and, when performed with a frequency of 10 repetitions every 2 hours throughout the day, may provide an ongoing stimulus that up regulates the immune response. One study reported that 12 weeks of light intensity tai chi exercises enhanced regulatory T cell function and anti-inflammatory cytokine production (45). Another study showed that progressive, moderate intensity exercise has a beneficial effect on natural killer T cell numbers, up-regulates T-helper cell mediated immune functions, and reduces the risk of infection and autoimmune disease in elderly people (46).

Our major observation in this study is that following McKenzie exercises there was a significant increase in the production of pro-inflammatory cytokines (IL-8 and TNF-α) ($p<0.05$) (Figure 2). Numerous studies report overexpression of TNF-α, IL-1α, and/or IL-1β, IFN-γ and IL-6 in patients with protruded, extruded, or sequestered intervertebral disc tissues (14, 15, 47-50). Animal studies also confirm the role of these cytokines in mediating pain (51-54).

Our study reported intercellular cytokine results that demonstrated increased levels (CD3+IL-8+ and CD3+TNF-α+ T cells; $p<0.05$), even following McKenzie exercises, in contrast to lower pain scores reported by all patients. The absence of a relationship between pain scores and intercellular pro-inflammatory cytokines level in this study was statistically insignificant, possibly due to the small sample size. However, in their study Kraychete et al. did not find any correlation between blood serum levels of TNF-α or IL-6 and pain intensity, or the duration of pain among patients with low back pain (55). In contrast, Koch et al. reported that the serum level of proinflammatory cytokine (IL-1-β, IL-2, IL-6, IFN-γ and TNFα) correlated significantly with increased pain intensity in patients experiencing chronic pain (56).

Following McKenzie exercises, the percentage of CD3+ cells expressing IL-1β and IL-6 was not significantly altered; these pro-inflammatory cytokines mediate pain. However, it is worth mentioning that IL-6

has both pro-inflammatory and anti-inflammatory properties (13). IL-1β excites the nociceptive dorsal root ganglia (57), increases the production of substance P and prostaglandin E2 by neuronal and glial cells (58, 59), and causes hyperalgesia.

There was a slight, insignificant elevation in the percentage of CD3+IL-13+ T cells following McKenzie exercises (Figure 3). IL-13 is an anti-inflammatory cytokine that down-regulates the production of TNF, IL-1, IL-8, and macrophage inflammatory protein (MIP-1α) by monocytes and, therefore, the inflammatory source of pain (60, 61). It was interesting to observe that the level of the anti-inflammatory cytokine, IL-4, increased significantly after 4 weeks of McKenzie exercises ($p<0.05$) compared to the baseline. IL-4 has a strong inhibitory effect on the expression and release of pro-inflammatory cytokines. The release of IL-4 suppresses monocyte-derived pro-inflammatory cytokines, including IL-1, TNF-α IL-6, IL-8, as well as the production of MIP and macrophage-derived nitric oxide (13). IL-4 also enhances the synthesis of the cytokine inhibitor IL-1rα, which, in turn, blocks the action of IL-1α and IL-1β (13). Again, the increase in anti-inflammatory cytokines IL-4 observed in the present study did not correlate with a reduced pain score.

It is difficult, from these preliminary results, to attribute all the immune regulation to the mechanical effect of the McKenzie directional preference exercises. The increased level of both pro-inflammatory IL-8 and anti-inflammatory IL-4 cytokines following exercise may also reflect the natural human immunoregulatory responses to re-establish the homeostasis between pro-inflammatory and anti-inflammatory cytokines (1, 2). However, it is possible that the significant increment in IL-8 following exercise may be caused by the ongoing inflammatory status of the deranged intervertebral disc, caused by muscle spasm and excessive postural and mechanical stresses throughout the day. The increment of anti-inflammatory IL-4 cytokines following intervention may possibly suggest that McKenzie exercises accelerate the up regulating of the anti-inflammatory cytokines.

Further, recent studies have demonstrated that low intensity exercise, such as walking 10,000 steps/day 3/week may enhance phenotypic switching of the macrophage (M1 to M2) (62-64). This may suggest that low intensity exercise, such as McKenzie exercises, may boost the M2 polarization, and thus constitute a novel exercise anti-inflammatory effect (64). Furthermore, M2a macrophage phenotypes are specifically involved in the resolution of inflammation and tissue repair process. Therefore, our preliminary results may suggest a possible long-term effect on systemic responses, which is driving the repair process in the patients undergoing McKenzie exercises in the long term. It is worth saying that the phenotype polarization of Ml to M2a macrophages occurs after exposure to IL-4 or IL-13 (65). Our preliminary results also demonstrate a systemic change in lymphocyte subsets, which may suggest a strong immune-regulatory shift following Mckenzie exercises.

On the basis of our preliminary findings, we suggest that McKenzie directional preference exercises may relieve pain by two different consecutive mechanisms. First, pain may be diminished initially by mechanical mechanisms, as explained by the concept of the disc dynamic model, i.e. relocation of the nucleus pulposus material in response to the precise McKenzie directional preference exercises (3, 5-9, 12). This would initially eliminate the pressure on the richly innervated nociceptive structures, including the outer annular fibers, posterior longitudinal ligament, dorsal root ganglia, and nerve root dural sleeves. Secondly, McKenzie exercises may help in stimulating and up regulating the anti-inflammatory cytokines, such as

IL-4 and IL-13, and therefore relieve pain in the long term.

Our results however, must be interpreted in the light of several limitations, including: the small sample size, the possible confounding effect of other anti-inflammatory biomarkers not explored in this study, patients' compliance with the study protocol, i.e. whether or not they took any pain medication, and whether they complied with the frequency of the prescribed home exercises. Another limitation is the absence of a control group. as we find it unethical to withhold treatment from patients with acute pain for a period of 4 weeks, or accepting patients as a control group receiving simple non-steroidal anti-inflammatory drugs which affect the immune-regulatory process and confound the results. Accordingly, further studies are needed to shed light on the therapeutic role of specific exercises used in physical therapy to treat low back pain, such as the McKenzie exercises, and to determine their role in stimulating favorable anti-inflammatory cytokine responses.

Conclusions

Four weeks of McKenzie exercise interventions significantly relieved back pain in patients with acute low back pain, induced an immune activation state with increase in pro-inflammatory cytokines, IL8 and TNFα, with a consequent increase in the anti-inflammatory cytokine, IL4, which may enhance and maintain pain relief in the long term.

Acknowledgements: This project was funded by the Kuwait University Research Administration (Grant No.NP01/08)

Authors' contributions: Conception and design: SAD, FM; Acquisition, analysis and interpretation of data: SAD, FM; Drafting the article SAD, FM; Revising it critically for important intellectual content: SAD, FM.

Conflict of interest: The authors declare that they have no conflict of interest.

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Original article

Acta Medica Academica 2014;43(1):30-34
DOI: 10.5644/ama2006-124.97

International textbook of family medicine: The application of EURACT teaching agenda

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Received: 9 September 2013
Accepted: 19 December 2013

The paper describes experiences in the development of an international textbook of family medicine. The process of its development has started in Slovenia, where the Slovenian authors have written a textbook, adhering strictly to the European definition of family medicine and its core competencies. The format and the approach were also adopted by Croatian authors, who have used most of the material from the Slovenian book, but have modified some of the chapters according to the situation in the country and have added some of their own. This activity has created an opportunity for a truly international collaboration in the area of education of family medicine, with a creation of an international consortium, which would be responsible for the core content of the book and local adaptations of the book according to the specificities and needs of different countries. **Conclusion.** This innovative approach in the development of teaching material may be interesting for a variety of smaller countries in Europe and worldwide.

Key words: Education-materials, Textbook, Family medicine, Slovenia, Croatia.

Introduction

Students need quality teaching materials that would cover the topic they are studying. This requirement is usually achieved by writing a comprehensive textbook on a subject. In this respect, family medicine is in a specific situation. Because of the breadth of the topic, writing a comprehensive book is a big task that can be achieved only by a large group of experts. Small countries may find it difficult to find individuals with expertise on all the broad areas of family medicine and their results are either a comprehensive textbook with varied quality of chapters or a textbook that does not cover all the elements of the discipline. The third solution is to translate a textbook from a foreign language, which poses another problem: the discipline of family medicine is country-specific and all the chapters can not be adequately used in all the countries. Specificities regarding culture, social and religious values, needs

of population, social determinants of health and differences in health care system all influence the way family medicine is practiced in every country. Family doctors and their educators need to take this into consideration.

EURACT, the European academy of teachers of family medicine, has developed a document that would enable family medicine educators to adress the area of family medicine comprehensively. The EURACT teaching agenda is a document, based on the European definition of general practice/ family medicine. The definition describes the 11 charactersitics of family medicine and lists six core competencies. One of the key characteristics of family medicine is the need of the physician to take into consideration the context in which he/she works (1). The agenda document was developed as an aid in developing teaching of family medicine (2). One of the potential applications of the document was also the development of a comprehensive textbook in family medicine.

The aim of this paper is to describe the experiences in developing that kind of a textbook in partnership of two countries with different health care systems.

The Slovenian situation

In Slovenia, the first comprehensive textbook of family medicine was written in 1992 (3). The aim of the first textbook was to define the core principles of family medicine. Its main aim was to demonstrate that the discipline of family medicine is different from the others. The textbook was very successful in this respect: it has described the main features that differentiate family medicine form other disciplines and was very successful in persuading the officials at the medical faculty in Ljubljana that family medicine has a specific contribution to education of future doctors, which resulted in the creation of a department of family medicine in 1994. Nevertheless, the textbook itself did not cover a lot of areas that were needed in teaching future doctors. Ten years later, the second textbook was produced (4). The ambition of the editors was to show the breadth of the discipline by covering all the aspects of family medicine, from clinical to organisational and attitudinal. The result was a large book with chapters of varied quality. Even if the editors went at great length to ensure good quality of the material, it became obvious that one could not find enough experts within family medicine in a small country, that would made it possible to write a comprehensive textbook. In 2012, the decision was made to write the third textbook. For this attempt, the editors have decided to follow these principles:

1. The textbook will be organised according to the European definition of family medicine and the EURACT teaching agenda (1, 2). The sections of the book will correspond roughly to the core competencies of family medicine, described in the document.
2. The clinical section of the book will cover only the clinical topics where there is a specific approach by a family doctor or where clinical topics are not encountered at secondary level. We have also limited ourselves to topics where we could provide our own original research or established experts.
3. The structure of every chapter was clearly defined. Each chapter was written as an explanation of a case in practice, so that the reader would follow how the principles in the chapter reflect themselves in the particular case.
4. The textbook would be aimed specifically at undergraduate medical students. It should be easy to use and relatively inexpensive, so the students could afford it.

With this in mind, a textbook of 32 chapters, organised in eight sections was developed (5).

The Croatian situation

In Croatia, the first comprehensive textbook of family medicine was written in 1986 (6). The second edition of textbook was published in 1992 and the third in 2000 (7). The aim of the first textbook was the same as in Slovenian example, i.e. to define the core principles of family medicine. This textbook was written into two parts. The first part was focused on main principles and specifities of family medicine as well as on organisational aspects. The second part was focused on specific clinical problems which occured in family medicine. In fact there was no natural relation among these two parts and students faced with the problem of recognizing and applying principles of family medicine in clinical problems solving. The need for writing new, modern textbook of family medicine was often discussed during regular annual meetings of all four departments of family medicine from Croatia. The close cooperation with departments of family medicine from Slovenia resulted with the initiative for the development of an international textbook of family medicine.

Cooperation with Croatia

After the textbook was almost finished, the contact with Croatian potential partners was established through the Split initiative. A partnership was developed according to the following principles:

- The format of the book and the format of the chapters should be the same
- Some chapters may be simply translated, but if it is necessary, adaptations of the chapters are possible. In that case, the Croatian author and the Slovenian author are co-authors of the chapter
- New chapters may be added
- The editorial process is done by two editors: the Croatian and the Slovenian.
- All the chapters need to be reviewed by original authors in case of adaptations. For new chapters, the Slovenian editor serves as the reviewer.

Based on these principles, the Croatian text was developed. The Croatian textbook contains 42 chapters, most of them are adapted from Slovenian authors, and some are added (Table).

Table Chapters of the Slovenian and Croatian textbook

Section title	Slovenian textbook	Croatian textbook
Introduction	Theory of family medicine	Theory of family medicine
	–	Development of family medicine in Croatia
	–	Position and functioning of family medicine in Croatia
Diseases, signs and symptoms	Low back pain	Low back pain
	Chest pain	Chest pain
	Aacute respiratory infections	Acute respiratory infections
	Urinary tract infections	Urinary tract infections
	Arterial hypertension	Arterial hypertension
	Diabetes	Diabetes
	Depression	Depression
	–	Chronic opstructive pulmonary disease
	–	Common skin disorders
	–	The most frequent anemias in family medicine
	Alcohol dependence	Alcohol dependence
	–	Drug dependence
	Medically unexplained sysptoms	Medically unexplained sysptoms

Table (continued).

Section title	Slovenian textbook	Croatian textbook
Practice organisation	Practice organisation	Practice organisation
	Health centre	Health centre
	Patient management	Patient management
Person-centered care	Principles of communication	Principles of communication
	Communication in practice	Communication in practice
	Counselling	Counselling
Specific problem solving skills	Decision making in family medicine	Decision making in family medicine
	Home care	Home care
	Referrals	Referrals
	–	Drug prescribing
	Emergency services	Emergency services
Comprehensive approach	Principles of prevention	Principles of prevention
	Preventive programmes	Preventive programmes
	–	Total cardiovascular risk
	Lifestyle	Lifestyle
	–	Primary health care of preschool children in family medicine
	Multimorbidity	Multimorbidity
	Palliative care and dying	Palliative care and dying
Community orientation	Health policy	Health policy
	Family	Family
	Family violence	Family violence
	Medical anthropology in family medicine	Medical anthropology in family medicine
	–	Specifities of family medicine in rural areas and islands
Quality	Evidence based medicine	Evidence based medicine
	Quality assurance	Quality assurance
	Professionalism and excellence	Professionalism and excellence

Discussion

The strengths of this innovative approach are in the fact that we were able to develop a model how the European definition and the EURACT teaching agenda can be applied on an example of a textbook of family medicine and to preserve its flexibility.

The potential opportunities of this activity are exciting. Based on the experience we have had with this activity, we have developed a framework that would enable other countries to join. The challenge of translating the core documents into English and offer it to the world community of educators in family medicine is an especially exciting one. The outlines of the framework are as follows:

1. The textbook will be managed by an international consortium of editors. There will be one editor per country. The editors of the project will be the persons who have already implemented the textbook in their own countries
2. The »core version« of the textbook will be written in English in order to ensure easy collaboration between different coutries regardless the native language. The »core version« will include chapters that the editors decide are of adequate quality and are co-authored by at least two authors from different countries.
3. When a country is willing to join the project, its representative will have to sign a written agreement with the consortium, which will stipulate the technical, finan-

cial and academic consequences of this collaboration. The country will then decide which chapters of the textbook will be used and which not. The decision of new chapters will be done in collaboration with the editors of the international textbook. All the modified chapters and the new chapters will be translated to English and the editors will decide which of them warrant to become part of the international textbook.

The future of the project depends largely on the possibility to have other partners that would be able to join this activity. The coordination of different countries will certainly become a challenge if the partnership grows.

There were many challenges in the process, mainly relating to the coordination of the editorial process, translations and technical problems. Understanding the differences in health care systems and procedures in different countries was a challenge in itself. Nevertheless, the agreement is that the positive results of the cooperation far outnumber the potential problems due to the coordination of services. It is much easier to work according to the pre-determined structure and to adapt the already existing text than to rewrite the new chapter from the beginning.

Conclusion

This exciting activity is to our knowledge the only approach of that kind in the area of medical textbooks. It has a potential to become an example of international academic collaboration in the field of family medicine. It is also the first product of the Split initiative, a project that has started two years ago in Croatia. Informal contacts with representatives of other countries make us believe that this is just a start of the process of international cooperation in the area of education of family medicine in Europe.

Authors' contributions: Conception and design: IŠ; Acquisition, analysis and interpretation of data: IŠ, MK; Drafting the article: IŠ, MK; Revising it critically for important intellectual content: IŠ, MK.

Conflict of interest: The authors declare that they have no conflict of interest.

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Original article

Acta Medica Academica 2014;43(1):35-39
DOI: 10.5644/ama2006-124.98

Satisfaction with the program of school bullying prevention and mental health promotion – Cross sectional study among primary school pupils in Mostar

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Received: 27 September 2013
Accepted: 14 March 2014

Objective. The aim of this study was to assess the frequency of experience in school bullying and family violence, satisfaction with the preventive-promotional program, knowledge about methods for opposing violence and attitudes toward the role of the family physician in bullying prevention. **Materials and methods.** The project was conducted by family physicians, nurses and sixth year medical students. The target group were 5th to 8th grade pupils of two primary schools randomly selected by computer. Basic information about the presence and types of bullying, the long-term consequences of violence and methods to oppose violent behavior was given as an interactive lecture to large groups of pupils. After the lecture, pupils received questionnaires about their experience of school violence, satisfaction with the program and their opinion about the role of the family physician in bullying prevention. **Results.** The results of the short term outcome evaluation of the program show that younger pupils evaluate the program better than older ones. Furthermore, we found that the frequency of experienced violence is not connected with satisfaction with the program. **Conclusion.** Most students have never experienced violence in schools and families, 5th and 6th grade students showed greater satisfaction with training, better knowledge of help in case of violence and a more positive attitude towards medical help. We found no significant differences in pupil's satisfaction with the program, knowledge about methods of opposing violence and attitudes towards the role of the family physician in bullying prevention, in relation to the frequency of experience of family violence and school violence.

Key words: Family medicine, Promotion, Prevention, School violence.

Introduction

Bullying is defined as repeated, negative acts committed by one or more children against another child. It may be physical or verbal (hitting or kicking, teasing or taunting), or may involve indirect actions such as manipulation in friendships or intentional exclusion of other children from activities. One of its main characteristics is an imbalance in real or perceived power between the bully and the victim (1). Bullying is a highly prevalent phenomenon with harmful and long-lasting effects on victims and a negative impact on the school climate (2). Recent studies con-

ducted among primary school pupils in Western Herzegovina show that 16% of children in early adolescence experience at least one form of bullying almost every day (3).

This article describes a prevention-promotional program named „For a life without violence" carried out by family physicians. The project is designed to reduce the level of bullying and related antisocial behaviors in children attending two urban primary schools in Mostar (4). Our prior study showed that schools in Mostar have high rates of school violence, as reflected by a high level of trauma symptoms in bullied pupils (5). Our Department of Family Medicine plans to start an intensive evidence-based multidisciplinary intervention program, targeting younger primary school pupils and the families of pupils involved in bullying.

The aim of our program was to compare awareness and knowledge of violence, coping strategies, attitudes toward the role of family physicians in bullying prevention amongst children that were involved in bullying and those that were not.

Materials and methods

According to the presence of school violence in primary schools and the high level of trauma symptoms in bullied pupils found in prior studies (4, 5), family physicians from the Department of Family Medicine organized the program in school violence prevention and mental health promotion (3).

The program was conducted in two primary schools in Mostar during April 2010 as a preventive and promotional project. The schools were selected as suitable. The program was organized by the Department of Family Medicine of the Medical Faculty, the University of Mostar in cooperation with the Health Care Center of Mostar.

The educators were family physicians, nurses of family medicine and 6th year medical students who have experience in lecturing. They had two days education about prevention and early recognition of domestic and school violence. The program was led by a team of experienced experts in this professional field. Participants in the program were pupils from the 5th to 8th grades of primary schools. The pupils were divided into groups of 5th, 6th, 7th, and 8th grades. Each group heard an interactive lecture about types of violence, psychological distress in victims of violence, coping strategies and the role of teachers, family members and family physicians in resolving the problem of school bullying. Brochures with information about school violence and community violence solutions were given to pupils. Immediately after the lecture, all the pupils filled out anonymous questionnaires. The questions were related to demographics, the frequency of experiencing violence at school and home, the frequency of violent behavior, satisfaction with the program, knowledge about methods of opposing violence, and attitudes towards the role of family physicians in the early recognition and prevention of school bullying.

The questions about experience of violence contained answers given on a 3-point Likert scale, as follows: 1 – never, 2 – sometimes, 3 – almost every day. The questions about satisfaction, knowledge and attitudes contained answers given on a 5-point scale, as follows: 1) absolutely disagree 2) disagree 3) partially agree 4) agree 5) fully agree. The questionnaire was created by the project managers. The questions about school violence are based upon the revised Bully/Victim form created in 1994 by Olweus (6), developed in 2003, and validated in 2007 (7).

For the purpose of this study, we analyzed data from a total of 630 questionnaires collected in two suitable, selected schools. All pupils in the selected classes participated in the program. In fact, nobody refused participation. Overall 299 (48%) male and 327 (62%) female pupils participated in the study. There was approximately an equal percent-

age (25%) of pupils in years 5th, 6th, 7th, and 8th. For statistical analysis the pupils were grouped into a pre-pubertal group (5th and 6th class), and a pubertal group (7th and 8th class).

Ethics

The study was approved by the Ethics Committee of the Medical Faculty of the University of Mostar and by the county Ministry of Education, Science, Culture and Sport. The authors of the questionnaire endorsed its usage, the school principals supported the investigation, and the examinees consented to participate with parental consent.

Statistics

A computerized database was formed using Microsoft Excel (version 11th Microsoft Corporation, Redmond, WA, USA). Statistical analysis was performed with SPSS for Windows, version 13.0 (SPSS Inc., Chicago, Illinois, USA). Differences between groups in continuous variables were tested with the Mann-Whitney U test and Kruskal-Wallis test. For the analysis of nominal variables the $\chi 2$ test was used for trends. The differences between groups were accepted as statistically significant at $p<0.05$.

Results

Out of the 626 pupils, 118 or 18.8% of the pupils were being bullied almost every day, 139 or 22.2% sometimes, but most of the pupils, 369 or 59%, had never been bullied at school (χ^2 test=185.85; $p<0.001$). Most of the students had never experienced family violence (88.7%), 7.3% answered that they experienced family violence sometimes, while 4% students suffer from family violence almost every day (χ^2 test=863.29; $p<0.001$).

Secondly, we asked pupils about their satisfaction with the preventive-promotional program. We found that younger pupils in 5th and 6th grades were more satisfied with the program, had better knowledge about methods of opposing violence and more positive attitudes towards the role of family physicians in bullying prevention than those in 7th and 8th grades (Table 1).

Based on an analysis of pupils according to the frequency of their experience school violence, we found no significant differences in satisfaction with the program, knowledge about methods for opposing violence and attitudes towards the role of family physicians in bullying prevention (Table 2).

There were no significant differences in the pupils' satisfaction with the program,

Table 1 Satisfaction of pupils with the program, knowledge about methods for opposing violence, and attitudes towards the role of family physicians in bullying prevention, according to grade

Variable	Points on the scale (range 1-5) according to grade		p
	5th and 6th grade	7th and 8th grade	
Pupils satisfaction with the program	4.5 (1)	4.0 (1)	<0.001
Knowledge about methods for opposing violence	4.5 (1)	4.0 (1.5)	<0.001
Attitudes towards the role of family physicians in bullying prevention	4.3 (1.6)	3.6 (1.6)	<0.001

Table 2 Satisfaction of pupils with the program, knowledge about methods for opposing violence, attitudes towards the role of family physicians in bullying prevention, according to experience of school violence

Variable	Points on the scale (range 1-5) according to experience of school violence			p
	Never	Sometimes	Almost every day	
Pupils satisfaction with the program	4.0 (3.5)	4.5 (1)	4.5 (1.5)	0.218
Knowledge about methods for opposing violence	4.0 (2)	4.5 (1)	4.5 (1)	0.369
Attitudes towards the role of family physicians in bullying prevention	3.3 (2)	4.0 (1.6)	3.6 (2)	0.985

Table 3 Satisfaction of pupils with the program, knowledge about methods for opposing violence, attitudes towards the role of family physicians in bullying prevention, according to experience of family violence

Variable	Points on the scale (range 1-5) according to experience of family violence			p
	Never	Sometimes	Almost every day	
Pupils satisfaction with the program	4.0 (3.5)	4.5 (1)	4.5 (1.5)	0.28
Knowledge about methods for opposing violence	4.0 (2)	4.5 (1)	4.5 (1)	0.369
Attitudes towards the role of family physicians in bullying prevention	3.3 (2)	4.0 (1.6)	3.6 (2)	0.985

knowledge about methods of opposing violence and attitudes towards the role of family physicians in bullying prevention in relation to the frequency of experience of family violence (Table 3).

Discussion

In our study, 22.2% of pupils experienced violence rarely, but 18.8% experience it almost every day. There have been no systematic studies on school bullying in Bosnia and Herzegovina. A previous study conducted among West-Herzegovinian pupils found 14% of them reported bullying experiences, 4% assaulted their peers and 3% were bully/victims almost every day (3). More recent world-wide cross-sectional investigations show greater variability in the prevalence of bullying, ranging from 9%-54% (8-11).

Overall 4% of the investigated pupils experience home violence almost every day, 7.3% experience it sometimes, while 88.7% never suffer from home violence. Children, who are victims of domestic violence, accept violent behavior as an acceptable form of behavior in future life. Finkelshor emphasizes that children who suffer domestic violence are more frequently exposed to violence at school and in the community (12). These are very important data in planning and implementation of prevention programs.

Younger pupils in 5th and 6th grades were more satisfied with the preventive-promotional program than older pupils in 7th and 8th grades. Also they had significantly more knowledge about coping strategies and a more positive attitude towards the role of family physicians in bullying prevention. Results from a recent study suggest the more significantly positive impact of the Olweus anti-bullying prevention program on 7th grade females than 8th grade (8). A review of the effects of preventive school-based anti-bullying programs, also shows that the relative reduction in violent behavior was greater in elementary and high than in middle schools (13). This finding underlines the fact that health promotion and prevention are more effective in younger age groups than in groups of older students. Our results also show that a prevention-promotional program on a primary level affects bullied and non-bullied pupils equally (14, 15).

It is important to recognize that all young people need support and education (i.e., primary prevention efforts) about relationship issues, safety and conflict management. All pupils need the primary level, such as our program, but some pupils will need a secondary level of prevention and intervention or support services, to deal with the aggressive and violent behavior that is already being exhibited (6, 8, 16).

Limitations of the study

The primary limitation of the study is that the sample of schools which participated in the study was not randomly selected. Actually, the schools were selected as suitable. The second limitation is the lack of long term evaluation of this health-educational program.

Conclusion

Our results show that most students have never experienced violence in school and their families, students of 5th and 6th grade showed greater satisfaction with the training, better knowledge of help in case of violence and a more positive attitude towards medical help. We found no significant differences in pupils' satisfaction with the program, knowledge about methods of opposing violence and attitudes toward role of family physician in bullying prevention in relation to the frequency of experience of school violence or family violence.

Acknowledgements: We are grateful to the wonderful cooperation of the teachers and pupils of primary schools in Mostar. We also thank the Ministry of Health of the Federation of Bosnia and Herzegovina for financial support for the project.

Authors' contributions: Conception and design: ECO; Acquisition, analysis and interpretation of data: KZ; Drafting the article: ECO, KZ; Revising it critically for important intellectual content: AZ, OBM.

Conflict of interest: The authors declare that they have no conflict of interest.

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Original article

Acta Medica Academica 2014;43(1):40-49
DOI: 10.5644/ama2006-124.99

Final year medical students' understanding of family medicine

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Received: 19 June 2013
Accepted: 29 November 2013

Objective. The European Academy of Teachers in General Practice / Family Medicine (EURACT) has developed an educational agenda, the key document for teaching family medicine in Europe. The aim of our study was to find out how final year medical students at the beginning of their family medicine clerkship understand the discipline of family medicine. **Methods**. The attitudes toward family medicine were paraphrased and developed into a 164-item questionnaire, which was administered to 335 final-year medical students at the beginning of their clerkship. Using combinatorial optimization with genetic algorithms we selected 30 items which yielded the highest Cronbach alpha reliability coefficient. Finally, we performed a factor analysis to find which dimensions of family medicine were recognised by the students and compared them with the domains defined in the EURACT definition. **Results**. The 30-item questionnaire had a Cronbach alpha reliability coefficient of 0.919. The differences between male and female students were not very significant (p=0.061). With the factor analysis we recognised seven factors, belonging to three out of six domains of the EURACT educational agenda: primary care management, person-centeredness and comprehensive approach. **Conclusion**. Final-year medical students at the beginning of their family medicine clerkship understand some of the dimensions of family medicine rather well, but they are not aware of some important competences of family doctors. There is a necessity to teach students about specific problem solving skills and the importance of balance between the health needs of an individual patient and the community.

Key words: Family medicine, Medical students, Understanding of family medicine, EURACT Educational agenda.

Introduction

In the majority of European countries, general practice / family medicine (GP/FM) is a fundamental part of the health care system. General practice / family medicine is a professional and scientific discipline with its own definition and competences. The key document which explains the discipline is European Definition of Family Medicine (1). GP/FM is now taught in most medical schools in Europe and vocational training is mandatory in most countries; in some of them new programmes for vocational training have been recently introduced (2).

An FM clerkship can allow students to understand the importance of primary care and of the significance of the general practitioner's role in the healthcare system, and

may also influence their career choice (3). After classes in FM, students report an improvement of their knowledge and attitudes towards FM, they form a positive perception of primary care practice and may also change their perception about the professional demands of primary care physicians (4).

To fulfil the aims of FM teaching, the Academy of Teachers in Family Medicine (EURACT) developed the Educational Agenda, the key document on FM teaching in Europe (5). The agenda is written as an explanation of the core competences of FM. It also includes a template with a list of broader objectives, teaching methods and assessment tools for each of the competences.

There are some reports that the competences defined in the Educational Agenda are not understandable to medical students or to experienced general practitioners (6, 7). Students usually understand the clinical competences of family doctors (8), but fail to understand other competences of family doctors, such as long term care and patient centeredness (9, 10), community orientation (7) and medical leadership and management (11).

As teachers, we would like to know how our student at the beginning of our rotation understands the discipline and to adapt our teaching if the student's understanding of the discipline is not sufficient. The aim of our teaching is for students to know and value the broad spectrum of competences which are typical for FM.

Based on our previous analysis (12) we decided to enlarge the sample of students participating in the research and to try to analyse the statements in the questionnaire as a whole (not divided into competences according to the definition) by using a genetic algorithm based combinatorial optimization, and later, by factor analysis, to find out which dimensions of FM were recognised by the students. Genetic algorithms have already been used in medicine, mainly for image segmentation tasks, but also for feature selection and model optimization (13, 14, 15).

Methods

All final-year (6th year) students at the Medical Faculty in Ljubljana, who were at the beginning of their family medicine clerkship, were invited. Nobody refused participation. The questionnaire was distributed to 335 students; 112 (33.4%) male and 223 (66.6%) female students. 14 questionnaires (4.2%) were excluded from the analysis due to incomplete data. 321 questionnaires were included in further analysis. The questionnaires were distributed by teachers at the beginning of the family medicine clerkship.

Development of the draft questionnaire

The questionnaire about attitudes was developed specifically for the purpose of the study. In the first stage, the European definition of FM was distributed to a group of 30 experienced family physicians (teachers of FM, involved in the teaching process at the undergraduate level). They were asked to use their imagination in developing statements that would reflect attitudes about each of the core competences listed in the Educational Agenda (5).

The statements were collected and paraphrased by one of the researchers (MPS) and organized into a list of statements that could be used in a questionnaire. This draft questionnaire was then sent to the same group of teachers for comments. After the comments were received, two researchers (IS, MPS) independently assessed them. The formulation of the draft questionnaire was the result of a consensus meeting between the two researchers. There was no need for a third expert to sort out potential conflicts. The result of this process was a list of 164 statements.

A seven-point Likert scale measures agreement. A score of 1 means total disagreement and a score of 7 means total agreement. The draft questionnaire consisted of 164 statements based on the Educational Agenda. In order to ensure maximum confidentiality and anonymity, no social or demographical data except gender was collected. A detailed explanation of the development and validation of the draft questionnaire has already been published (12).

Selection of items for the final questionnaire using a genetic algorithm

To find the subset of questionnaire items with the largest possible Cronbach alpha coefficient, a search procedure called "combinatorial optimization" must be applied. One of the best combinatorial optimization methods is the genetic algorithm (GA) (16, 17, 18).

GA, which belongs to the larger class of evolutionary algorithms (EAs), is a robust optimization algorithm that mimics the natural evolution process. It uses evolutionary operators, such as inheritance, selection, mutation and crossover. In EAs, a problem may be viewed as an environment, and feasible solutions may be viewed as individuals living in this environment. Similar to natural evolution, where the fittest individuals generally tend to survive, the best solutions in an EA also tend to survive, create offspring and mutate in order to produce even better solutions.

Each potential solution may be viewed as a chromosome or genotype. It is usually a string, composed either of bits or real numbers. A population of chromosomes encode candidate solutions to an optimization task. The initial population consists of randomly generated chromosomes. Using evolutionary operators of selection, mutation and crossover, the next generations of the population are produced. On average, each subsequent generation consists of better chromosomes or solutions for the task. We are usually interested in the best chromosome that appears during the course of the algorithm, being the best solution so far.

For a GA an evaluation or fitness function must always be provided. It measures the quality of each chromosome, as a candidate solution to the specified problem. This is the only strictly problem-specific part of the genetic algorithm. The others may be more or less generic.

In our case, a chromosome encodes which items are present in the itemset. Since we are looking for the best of all the itemsets of a particular size, a fixed number of bits has the value of 1. In this case it is not possible to mutate bits in a random manner, since the number of items may change. What we need is a mutation that performs only permutations on the chromosome. With some small probability (mutation probability) a randomly selected 1 is replaced by a randomly selected 0. Therefore, an item is replaced by some other item. The crossover operation is more tricky and will not be described here.

Our goal was to find a subset of the questionnaire items that would yield the highest possible Cronbach alpha coefficient. On the other hand, it is known that larger subsets yield larger alpha values. As a reasonable size for the questionnaire (the number of items) we chose 30.

The size of the search space (the number of all possibilities) is huge. It amounts to

$$\binom{164}{30} \approx 7 \cdot 10^{32},$$

which is the number of different 30-item subsets out of a 164-item set. It is obvious that no method is guaranteed to produce the optimal solution. However, the GA usually finds near-optimal solutions. The value of the alpha of a candidate subset serves as the evaluation function of the corresponding chromosome.

Basic data analysis

We used descriptive statistics: mean values of Likert scale values with standard deviation (SD) for the description of item values and independent sample t-test (two-sided) to compare the total score of the questionnaire between male and female students. We considered a p value less than or equal to 0.05 to be significant.

Factor analysis

A principal component factor analysis with varimax rotation was performed to condense the attitudinal items that predict career choice in family medicine into a smaller number of coherent factors. Items that showed a minimum factor loading of 0.5 and factors with eigenvalue greater than 1 were retained.

Two independent researchers (MPS and IS) explained the meaning of the factors. The final explanation of the factors was the result of a consensus meeting between the two researchers, who had discussed the comments and made the final description of the factors. There was no need for a third expert to sort out a potential conflict.

Ethical approval

The study was presented to the national ethical committee and was given its approval.

Results

Description of the sample

We analysed the questionnaires of 321 final year medical students, 109 (34%) male and 212 (66%) female, at the beginning of their family medicine clerkship.

Description of the 30-item questionnaire

The genetic algorithm was run for 1000 generations, with 500 chromosomes in the population. Using the genetic algorithm we found the best (or near best) 30-item questionnaire, regarding Cronbach alpha. The reliability of the questionnaire, assessed by Cronbach alpha was 0.919. The resulting items are presented in Table 1.

Table 1 The 30-item questionnaire

Item	Range	Mean	SD
Physicians should not transfer their professional responsibilities to others	1-7	6.08	1.09
High quality of primary care can save a lot of money	1-7	6.29	1.16
Without patients' cooperation, there is no success in treatment	1-7	6.44	1.01
Without good communication, one cannot work well in practice	1-7	6.42	0.87
A long term doctor-patient relationship improves the efficacy of work	1-7	5.89	1.07
There is no appropriate treatment without trust	1-7	6.17	1.09
The doctor should be objective	1-7	6.17	1.02
A good doctor listens to his patients	1-7	6.03	1.35
A good doctor empathises with the patient in distress	1-7	5.31	1.26
Detailed clarification of a patient's health care problems is important	1-7	6.06	1.10
Priorities of physicians may be different from priorities of patients	1-7	5.93	1.21
Treatment plan should be adapted to the patient	1-7	6.28	0.91
Priorities of patients' care may change	1-7	5.71	1.29
The patient's personality should be taken into account in treatment	1-7	5.63	1.28

Table 1 (continued)

Item	Range	Mean	SD
The psychological dimension of the disease is usually as important as the physical aspect	1-7	6.27	0.99
Advice for a healthier lifestyle is an important duty of the physician	1-7	6.38	1.06
Physicians educate by their own example	1-7	5.74	1.48
Palliative care is as important as active treatment	1-7	6.15	1.35
Prevention is a key to good health	1-7	5.76	1.38
For each patient one should include preventive advice	1-7	5.68	1.44
At each visit, one should include preventive advice	1-7	5.65	1.61
It is important that the doctor knows the legal limitations of his work	1-7	6.05	1.23
All patients should have the same level of care regardless of their social status	1-7	6.12	1.50
Physicians should adapt their working style to the needs and possibilities of the community where they work	1-7	5.58	1.16
Under given circumstances, physicians should provide the same level of care to all patients	1-7	6.55	0.88
Physicians should cooperate with the local community	1-7	5.76	1.29
Computerization helps to achieve a high quality of work	2-7	5.79	1.14
Physicians should know the legal framework of the health care system	1-7	5.89	1.21
Patients should know their rights and also their duties	1-7	6.14	1.40
If necessary, the family should be included in the treatment	1-7	6.14	1.13

The mean sum of all items was from 41 to 203, with a mean of 173.7 (SD 19.2). The differences between the male and the female students were not significant (t-test, p=0.061).

Factor analysis

Using the component factor analysis with varimax rotation we explained 57.3% of the total variance. The proportions of the variance explained by the particular factor after varimax rotation (rotation sums of squared loading) is presented in Table 2.

Table 2 The proportions of the explained variance

Component	Eigenvalue	% of Variance	Cumulative %
1	4.30	14.33	14.33
2	2.36	7.98	22.31
3	2.34	7.81	30.13
4	2.31	7.68	37.81
5	2.27	7.65	45.46
6	2.14	7.15	52.61
7	1.41	4.70	57.31

Table 3 presents the items, classified by factor analysis. Items with loading of 0.5 or more and the component to which the item belongs were bolded. Six items had loading of less than 0.5.

Based on the factor analysis, we identified seven factors explaining the students' understanding of FM. The first factor which explains most of the variability is related to prevention and palliative care. The factors are as listed:

1. Prevention/palliative care;
2. Social justice
3. Health care management
4. Person centeredness
5. Partnership/communication
6. Empathy
7. Financial efficacy

Table 4 shows the comparison of the students' understanding of the discipline with the competences of general practice/family medicine defined by the educational agenda. Students recognised three out of six competences quite well. They failed to recognise the competence of specific problem-solving skills, community orientation and the holistic approach.

Table 3 Rotated component matrix. Factors with loading greater than 0.5 are bolded

Item	Component						
	1	2	3	4	5	6	7
Prevention is a key to good health	**0.76**	0.02	-0.01	0.15	-0.08	0.23	0.15
For each patient one should include preventive advice	**0.74**	0.13	0.11	0.13	0.22	0.08	0.06
At each visit, one should include preventive advice	**0.70**	0.29	0.06	0.08	0.15	0.17	-0.06
Palliative care is as important as active treatment	**0.61**	-0.02	0.25	0.14	0.14	0.06	0.24
Physicians educate by their own example	**0.60**	0.20	-0.01	0.29	0.20	-0.08	-0.14
Patients should know their rights and also their duties	**0.59**	0.16	0.36	0.06	0.15	0.09	0.10
Advice for a healthier lifestyle is an important duty of the physician	**0.51**	0.38	0.13	0.06	0.26	0.26	0.24
Under given circumstances, physicians should provide the same level of care to all patients	0.24	**0.70**	0.21	0.21	0.05	0.11	-0.01
All patients should have the same level of care regardless of their social status	0.42	**0.56**	0.05	-0.13	0.04	0.18	0.06
The doctor should be objective	-0.06	**0.51**	0.14	0.34	0.28	-0.07	0.03
It is important that the doctor knows the legal limitations of his work	0.34	0.45	0.45	0.14	0.09	-0.06	0.19
The psychological dimension of the disease is usually as important as the physical aspect	0.22	0.43	0.11	0.22	0.25	0.41	0.19
Computerization helps to achieve high quality of work	0.31	0.00	**0.59**	0.06	-0.04	0.43	-0.00
Physicians should know the legal framework of the health care system	0.47	0.05	**0.61**	0.09	0.15	0.03	0.26
Priorities of physicians may be different from priorities of patients	-0.08	0.16	**0.55**	0.23	0.11	0.20	0.34
Physicians should adapt their working style to the needs and possibilities of the community where they work	0.04	0.20	**0.53**	0.19	0.27	-0.03	-0.14
Treatment plan should be adapted to the patient	0.11	0.09	0.24	**0.69**	0.18	0.14	0.05
Priorities of patients' care may change	0.30	0.25	0.28	**0.57**	0.04	0.00	0.14
Physicians should cooperate with the local community	0.33	0.09	0.16	**0.54**	-0.05	0.31	-0.25
Physicians should not transfer their professional responsibilities to others	0.29	0.07	-0.11	0.48	0.31	-0.00	0.30
Detailed clarification of patient's health care problems is important	0.11	0.37	-0.02	0.43	0.03	0.20	0.29
Without patients' cooperation, there is no success in treatment	0.27	0.09	0.13	0.13	**0.70**	-0.05	0.09
Without good communication, one cannot work well in practice	0.09	0.44	-0.01	0.31	**0.51**	0.19	0.03
There is no appropriate treatment without trust	0.14	0.00	0.22	0.08	**0.50**	0.37	0.28
A good doctor listens to his patients	0.22	0.22	0.12	-0.07	0.50	0.34	0.27
If necessary, the family should be included in treatment	0.17	0.24	0.43	0.08	0.47	0.23	-0.29
The patient's personality should be taken into account in treatment	0.05	0.13	0.22	0.01	0.02	**0.68**	0.24
A good doctor empathises with the patient in distress	0.20	0.09	-0.09	0.19	0.17	**0.62**	-0.08
A long term doctor-patient relationship improves the efficacy of work	0.04	-0.03	0.16	0.34	0.39	0.40	-0.04
High quality of primary care can save money	0.32	0.13	0.15	0.13	0.18	0.15	**0.63**

Table 4 Comparison between the competences of FM based on the EURACT Educational agenda and students' understanding of the discipline

Competences based on EURACT Educational agenda	Competences, recognised by final year medical students
Primary care management	Social justice (factor 2) Health care management (factor 3) Financial efficacy (factor 7)
Person-centered care	Person-centeredness (factor 4) Partnership / communication (factor 5) Empathy (factor 6)
Specific problem solving skills	–
Comprehensive approach	Prevention / Palliative care (factor 1)
Community orientation	–
Holistic approach	–

Discussion

Using combinatorial optimization with the genetic algorithm we selected 30 out of 164 items which yielded the highest reliability. Using the factor analysis we recognised seven factors which belong to three of six in the EURACT Educational Agenda predefined competences of FM. Based on our analysis we found that students understand the competences of primary care management, person-centered care and comprehensive approach quite well, but they are not aware of specific decision making processes, the importance of balance between the needs of individual patients and the community, and the concept of holism.

All the items in the 30-item questionnaire had positive connotation and expected answers were closer to 7 than 1. However some students answered certain questions negatively. The reasons might be a lack of student motivation for completing the questionnaire, which was originally long and time consuming (12), or a lack of understanding of the discipline at the beginning of their FM clerkship. The participants had already had experience in hospital settings, but not necessarily experience in primary care. In hospital settings there are patients with severe illnesses, requiring a high intensity of care. There is inadequate opportunity during classroom learning to teach about care continuum, cost effectiveness, chronic disease management, family and patient perspectives and the impact of the social environment on illness (10).

Based on the sum of all the 30 items we found that generally the understanding of the discipline of FM in our sample of students was of an acceptable level. There were no gender differences in the perceived meaning of the discipline of FM. The clerkship in FM in the last year of their study is their first classroom learning in primary care (19), but with our results we confirmed that students generally obtain knowledge about primary health care from practical experience rather than from classroom learning (20).

Social justice, patient-centeredness, partnership, communication skills and empathy were factors recognised by the students that express the social role of family doctors. On the other hand, among the selected items there were no statements which belong to the competence "specific problem-solving skills", which cover the characteristics of the specific decision making process of family doctors and present a key characteristic of the family doctor as a medical expert.

Based on our analyses we could confirm the findings from the research about medical students' attitudes toward FM, that students value the social role of family medicine and family doctors more than their scientific value (21). We could add that students also recognise the importance of organisational and management skills of family doctors and recognise them as teachers in organisational and management skills. In a systematic review it was found that students recognised the need to develop leadership and

management competences, since relatively little emphasis was placed on leadership and management in medical curricula (11).

Students did not recognise the important role of family doctors in incorporating the community in the management of patients. Hospital based learning was focused on biomedical knowledge necessary for treating acute ill patients, but long-term care of chronically ill patients should be patient-centered and should take the community into account as well as the individual patient (10).

Students also failed to recognise that the holistic approach to patients is one of the most important characteristics of FM. The concept of holism is multidimensional and might be misunderstood as complementary and alternative medicine (6). Specific teaching methods exist by which the holistic approach may be taught (watching movies, students' letter to patients) (22, 23). These methods were not used in previous education programs.

When comparing our results to the results of other studies, we were able to confirm that students understand the clinical competences of family doctors (8), but fail to understand some other competences of family doctors (7, 9-11). In a qualitative research synthesis about medical students' perception of and attitudes towards family medicine, it was found that most of the included studies describe factors which influence a career choice for family medicine (24). The correlation between understanding of the importance of primary care and the significance of the general practitioner's role in the healthcare system and career choice was detected (25). Positive perceptions regarding the possibility of having long term doctor-patient relationships and of treating complex disease patterns when working as a family physician, appears to be associated with the attractiveness of a career in family practice (26).

Strengths and limitations

The study was conducted on a representative sample of final-year medical students at the beginning of the FM clerkship. The questionnaire was developed specifically for the purpose of the study, adhering to the principles of qualitative research. The genetic algorithm is one of the best and most robust combinatorial optimisation methods. We could hardly expect a subset of items with much higher reliability than what we achieved.

Our study also has several limitations. We included only students of one of the two medical faculties in the country. Due to the slightly different curriculum of the Medical School in Maribor, their students could have a different understanding of the discipline at the beginning of their FM clerkship. Due to the cross-sectional design of the study we did not have to estimate some important aspects of reliability and validity, including test-retest reliability or responsiveness to changes.

Students answered the selected items with the whole range of possible answers (from 1 to 7), but the mean scores of the items were closer to the maximal value, since all the items had positive connotation, potentially leading to an "acquiescence" response style and possibly causing the result to be more positive regarding the understanding of family medicine. Some of the items included in the factor analysis had loading below the acceptable level and were not taken into account in the explanation of factors. On the other hand, based on the factor analysis, some of the factors consisted of items, which were contextually not suited to the other items in the factor and should be considered as non-classified items.

Implications for practice

Medical students should be taught the unrecognised competences of family doctors as part of the FM curriculum. As teachers

we should adapt our curricula to address the competences which were not recognised by the students. Combining professional knowledge with a broad concept of humanistic personal development is a never-ending story and an important issue for medical schools in general, and some efforts have been already made at our Medical Faculty (27, 28).

In the seven-week clerkship of FM at Ljubljana faculty (29) we have to have a realistic view about the in depth understanding of some very complex concepts such as the holistic approach, which is sometimes difficult to understand even for experienced doctors. We are also aware that to understand specific problem-solving skills and community orientation, some more experience working in FM and close and long-term contact with patients is required (10, 30), but the clerkship should offer at least a basic understanding of these competences.

It would be interesting to check the students' understanding of the discipline after the implementation of our traditional curriculum of FM and after the adaptation based on our analyses, in order to see the influence of the adapted curriculum.

Implication for research

It would be interesting to know how experienced family doctors understand the discipline. There were some reports that even family doctors have a problem understanding the concept of holism. Family doctors' understanding of the discipline could be a template for adaptation of the EURACT definition of general practice /family medicine. It seems that the concept of holism is not a separate competence, but a general concept and covers the other five competences.

Conclusion

Final-year medical students at the beginning of their family medicine clerkship understand some of the dimensions of family medicine well, but they are not aware of some important competences of family doctors. There is a need to teach students about specific problem-solving skills and the importance of balance between the health needs of an individual patient and the community.

Acknowledgments: The authors would like to thank the team of the Ljubljana family medicine department for their valuable input in the creation of ideas for the questionnaire and to the students who completed the questionnaire.

Authors' contributions: Conception and design: MPŠ, IŠ and BŠ; Acquisition, analysis, and interpretation of data: MPŠ, BŠ; Drafting the article: MPŠ, BŠ; Revising it critically for important intellectual content: IŠ, BŠ.

Conflict of interest: The authors declare that they have no conflict of interest.

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Original professional article

Acta Medica Academica 2014;43(1):50-62
DOI: 10.5644/ama2006-124.100

Teaching science throughout the six-year medical curriculum: Two-year experience from the University of Split School of Medicine, Split, Croatia

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Received: 13 August 2013
Accepted: 11 November 2013

Objective. The aim of this article is to present the introduction of a mandatory, vertically integrated course in research methodology into medical curriculum. At the School of Medicine in Split (Croatia) we organized this course in 2010, with the total of 270 hours in the 6-year curriculum. In the first year (50 hours) students learned basic principles of scientific method, structure of scientific article, basic statistical concepts, data analysis, interpretation and presentation. In the second year (25 hours) students applied the knowledge from the first year in real examples of research data to answer a research hypothesis and present the results and conclusions. Students were guided through the process of making a hypothesis, analyzing data, interpreting them, constructing tables and figures, and writing a short research report. At the end of the course they formally presented the results to other students and course teachers, using PowerPoint slides. The third year (25 hours) was devoted to mastering concepts and basic skills of evidence-based medicine (EBM). The course in the fourth year (25 hours) was integrated with the clinical courses (internal medicine, neurology, and psychiatry) and structured as a "journal club". In the fifth year (25 hours), the teaching was devoted to developing a research plan for the graduation thesis that the students had to conduct during the sixth year. The sixth year (120 hours) was devoted to the execution of research planned in the fifth year, including data collection, data analysis, interpretation, and thesis writing and defense. **Conclusion**. The new course succeeded in increasing students' knowledge and skills for critical thinking and EBM, and prepared them for life-long learning in medicine.

Key words: Medical Education, Evidence-Based Medicine, Medical Research, Teaching Methods.

Introduction

"The first 2 years of medical school have got to be changed. Students are spending more and more time understanding the difficult aspects of molecular biology, but we are kidding ourselves to think they use their knowledge of DNA – in my day it was the Krebs cycle in making clinical decisions at the bedside. They do not. They make clinical decisions based on how the last patient did, how their friends are treating patients and what the latest article by an authority says they should do. And we have got repeated evidence now that the authorities are way behind with regard to the

data in clinical trials. In medical school, I think we have to just hammer away at evidence and probability theory and general statistics."

Dr. Thomas Chalmers, American physician who played a pivotal role in the scientific development of the randomized control trial and meta-analysis (1).

There is a growing recognition that the knowledge about research design, conduct and analysis is low in biomedicine, both in developing and developed countries (2-4). In small countries, this lack of knowledge is coupled with serious barriers to conducting research, such as the shortage of researchers who could generate critical mass of sustainable research output, financial restrictions, communication and language barriers (5-8). Despite strategies proposed to alleviate problems (5-8), research in most small and developing countries lags behind that in countries belonging to the so-called mainstream science (9).

Over the last 20 years, through our work as educators and editors of a general medical journal dedicated to publishing research from small scientific communities (10-12), we have also recognized that researchers from developing countries often lacked adequate training in critical assessment, research methodology and statistics. To address these problems in our own country and prevent them at their core we introduced obligatory science teaching in medical schools in Croatia.

The aim of this article is to present our experience in introducing a mandatory, vertically integrated course in research methodology into medical curriculum.

Science teaching in medical schools in Croatia

In 1996, to complement the existing courses of medical informatics and statistics, we had introduced a mandatory 25-hour course on research methodology, critical assessment and scientific writing into the curriculum of the University of Zagreb School of Medicine at the second year of a six-year medical program (13). In the following year, the course was accepted by other three medical schools in Croatia. The evaluation of our course in two observational cross-sectional studies, and a cohort study alongside a non-randomized trial showed a positive effect of the course on the students' knowledge and attitudes toward science (14-17).

In 2010, as part of Croatia's then upcoming ascension to the EU, all schools of medicine had to introduce new medical curriculums and satisfy the European Directive 2005/36/EC, which required that all medical students upon graduation have: "Adequate knowledge of science upon which medicine is based, and good comprehension of scientific methods, including the principles of biological functions and assessment of measuring biological functions, the evaluation of scientifically established facts and the analysis of data" (18, 19). Based on our previous experiences, and in line with the World Federation for Medical Education (WMFE) recommendations (20), we were successful in convincing the School of Medicine at the University of Split to introduce a longitudinal six-year mandatory teaching of science (21).

New science education at the School of Medicine in Split

In designing the program, alongside our previous experience with the second year mandatory course on scientific methodology, we relied on the basic principles of adult learning and the recommendations for designing medical courses (3, 23-33) (Supplementary table 1). We divided a total study load of 270 hours of teaching granted for the course in six smaller parts, and spread them longitudinally throughout the 6 years of an integrated

Table 1 Overview of the new vertically and horizontally integrated science course at the University of Split School of Medicine

Curriculum year (no. of class hours)	Teaching topics	Course outcomes
1st year (50)	• Principles of health research • Structure of research articles • Study designs • Principles of statistics: populations and samples, types of data, hypothesis testing, sources of error, data estimation, description, interpretation and presentation	• Writing of curriculum vitae according to the EU standard (Europass) • Writing of research abstract in English • Series of problem-oriented practicals in study design and statistics
2nd year (25)	• Short repetition of the first year • Data analysis and presentation • Writing research report	• Statistical analysis of a dataset according to specified research question • Brief written report on results • Oral presentation of results to colleagues and teachers
3rd year (25)	• Evidence based medicine (EBM) • EBM steps • Quality assessment in health care	• Answering a specific clinical question based on a given vignette (PICO question, literature search, critical assessment, decision)
4th year (25)	• "Journal clubs": critical reading of research papers with different study designs (cross-sectional, cohort and case-control studies, randomized controlled trials, systematic reviews), relevant to clinical rounds	• Answering a specific clinical question student encountered in his/hers clinical rounds (PICO question, literature search, critical assessment, decision)
5th year (25)	• Writing research proposal for diploma thesis (structured proposal addressing background research, research hypothesis, study design, sample size calculation, participants, ethical approval, intervention, main outcome measures, bias and confounding factors, statistical analysis, authorship and publication plan, financial support, conflict of interest declaration)	• Written research proposal for diploma (MD) thesis
6th year (120)	• Short repetition of the first five years Methodological counseling and support during all stages of research for diploma thesis	• Published thesis

medical curriculum, with horizontal integration of the topics with other courses at their respective individual curriculum years. Student groups for seminars ranged from 24-28, and for excercises from 11-14 students. Recommended literature encompassed two textbooks, both in Croatian and English (34, 35). Each year's main topics, outcomes and their evaluation methods are presented in Table 1, with a more detailed analysis presented in the following paragraphs.

The First Year

First year students are always shocked by the extent of material they need to absorb in during medical curriculum, even more so in Europe, as high-school/secondary education is most often followed directly by integrated six-year medical studies (36). Students thus tend to see research education, and "non-medical" courses in general, as an unnecessary burden that takes their precious time away from "more important" courses such as Anatomy, Physiology and Pathology. We have therefore allocated the first year's block, consisting of 50 hours (2 weeks) of teaching, at the very end of the first year. Starting with basic principles of scientific method and reasoning, the structure of scientific article, study designs and literature

search, students are gradually introduced to the basic statistical concepts, most notably data types, sample and population descriptors, sources of error, statistical tests, data analysis, and finally data interpretation and presentation. Knowledge and skills learned in the first year's block are evaluated through a series of practical tasks; these are marked and constitute 70% of the final grade, followed by a multiple-choice written test at the end of the course (30% of the final grade). At first, students were resistant toward any "mathematical" concepts discussed in the class. However, as they realized how these concepts helped explain everyday clinical problems and questions about health, they appreciated the problem solving exercises and became skilled in identifying study designs in published reports in proposing designs to address research questions during practical work.

The Second Year

The second year's block, consisting of 25 hours (one week) of teaching, was designed as practical application of knowledge from the first year to practical research problems. Students worked in groups of two; each group received a prepared de-individualized Excel database with individual data from a previously conducted research study and were instructed to answer a specific research question based on these data. During the 5 days of the course students were guided through the process of making a hypothesis, analyzing data, interpreting them, constructing tables and figures (minimum of one figure and one table), and writing a short research report. At the end of the course they formally presented the results to other students and course teachers, using PowerPoint slides. The course mark was based on the quality of their final research report and presentation of data (scored by two teachers who attended all presentations). The course proved to be intensive and demanding for students, but with teacher's time and assistance, as well as their encouragement, the initial anxiety of students about the complexity of the practical work was transformed into very proud presentations on the last day and satisfaction with the creative work performed.

The Third Year

The third year's course, consisting of 25 hours (one week) of teaching, was devoted to mastering concepts and basic skills of evidence-based medicine (EBM). During the first day, students were introduced to five basic steps of EBM: 1) asking focused questions, 2) finding evidence, 3) critical appraisal, 4) making a decision, and 5) evaluating performance. During practicals of the first day, they used their knowledge from previous years to calculate numbers needed to treat (NNT) from results of published clinical trials, and interpret those NNTs in the context of provided confidence intervals. During the second day, the students practiced formulating questions using a PICO format (Patient and Problem, Intervention, Comparison, Outcome) from cases presented as brief clinical vignettes. The next day, they used PICO to create a search strategy for PubMed and identify relevant studies with different study designs. The third day was focused on critical appraisals of a randomized controlled trial (RCT) related to individual PICO question, followed by critical appraisal of a systematic review questions on the fourth day. Critical appraisal sheets were used for each practical work (37). Each practical task was graded and constituted 70% of the final course grade, with a brief knowledge test on EBM at the end of the course (30% of the final grade). The vignettes for students were created based on existing systematic reviews in the Cochrane Collaboration Database of Systematic Reviews, to ensure that the stu-

dents would be able to find and appraise the best available evidence for their clinical question. Students were very responsive to this course and found it most relevant and useful for their medical studies, particularly as a preparation for the clinical part of the curriculum.

The Fourth Year

The fourth year course (25 hours), unlike the courses of the first three years, was integrated with the clinical courses (internal medicine, neurology, and psychiatry) and structured as a "journal club" (38). Each week 3 student-hours were dedicated to a single type of study design and detailed analysis of a paper about a cross-sectional study, cohort study, case-control study, randomized controlled trial and systematic review. Topics were chosen either by the students themselves or their clinical mentors. Our goal was to offer the opportunity to the students to acquaint themselves with research performed by the clinicians working in the University Hospital Center, as well as with papers that physicians regarded highly relevant for their everyday practice. Each "journal club" was graded, and the final exam was a task similar to that of the previous year, yet instead of a vignette we provided, the students had to identify a clinical question about an actual patient they encountered on their clinical rotations. The English language of the presented articles did not pose a problem for the students, as all Croatian students start learning English as their first foreign language from their first year of primary schools. Although we believed that the course structured as a "journal club" would add valuable content to students' morning clinical training, it proved too time-consuming for the students, and students felt that it took away the time needed for studying for the clinical course exam.

The Fifth Year

The fifth year's block, consisting of 25 hours (one week) of teaching was devoted to developing a research plan for the graduation thesis that the students had to conduct during the sixth year. Our previous experience suggested that the key reason for unsuccessful research, especially in clinical medicine is poor or incomplete planning (39, 40). We developed a checklist with 21 items, with precise instructions on what the students had to include in their research plan that was formally submitted as the protocol for their diploma work. The checklist included defining outcome measures, calculating sample size needed, and listing of authors, with perceived contributions for each author according to ICMJE authorship criteria (41). Students either developed their own research projects and later found mentors or selected research projects already offered by School's teachers. The actual plan of research was returned up to 3 times to students, with detailed written instructions (using track changes in a word processor) of what should be corrected and/or completed. Most common students' mistakes and difficulties in formulating research plans are presented in Table 2. The final mark of the course was composed of points evaluated for each item on the research plan. Writing of the plan was very valuable for the students' sixth year diploma work, as the students became aware of all phases of research study, as well as the level of quality that would be expected from their final graduation tasks. It was our impression that it was on this level of science education that students sincerely and fully comprehended what research was, what its function was and why it was so strenuous and yet at the same time exciting and rewarding.

Table 2 Teachers' experiences in supervising 5th year medical students during their writing of research proposals for their MD theses at the University of Split School of Medicine

Proposal item*	What was expected from students	What students usually wrote in the first draft and how they revised it
Title	Clear and concise indicative or informative title	Study design was usually not indicated; when it was added, students appreciate the precision of the title and said that seeing a clear title encouraged them for further work.
Scientific background	Short, focused description of the research field and existing evidence	Students tended to write too long and very general introductions. A lot of effort was needed to focus them on the actual problem that would be covered by the thesis.
Hypothesis	Explicit, clear and brief statement	Students tended to have too many hypotheses, discussing those hypotheses and primary objective of their research helped them focus on one or two most important outcomes.
Originality of research	Brief explanation whether the proposed research is original	Student defended the originality of their work by stressing the local relevance ("first in our country") and rarely planned to use analytical study designs.
Study design	Rationale for study design proposed	This section was most often poorly written, and the most common study design was a "retrospective study". Usually we had to discuss the research question in great detail to arrive at appropriate study design; this often lead to the revision of other items.
Sample	Detailed definition of the study sample, with inclusion and exclusion criteria	Most often these were already well explained in the first draft; more problems were encountered with epidemiological studies, where the population was often not clearly defined.
Sample size calculation	Calculation of the sample size, using statistical software of web-sites	Students mostly came to the teacher for advice before addressing this item. This task was very useful for them to clarify study design, study groups and outcome measures, as well as to review basic statistical concepts.
Subjects and methods	Concise description of the subjects and methods	Regularly well written. Students mostly needed to be reminded to refer to literature or manufacturers when they described the methods.
Primary outcome measure	Clear description	Regularly well written; sometimes students had to add measuring units.
Secondary outcome measures	Clear description	Very often students listed too many secondary outcome measures, and mentioned those they would not measure. Discussion was often needed to clarify the difference between primary and secondary outcome measures.
Potential sources of bias and confounding factors	List and explanation	Very hard concept for students; this was the part of the proposal that needed a lot of discussion and supervision.
Statistics	Description of the statistical analysis and data presentation	The statistical methods used are usually simple univariate statistics. The discussion with students helped them revisit basic statistical principles.
Expected results	Description of expected results in view of the proposed hypothesis and of the importance of results	This section was most often poorly written; students do not have clear concept of what would be the concrete result of their work.
Internal and external validity	Brief arguments for the validity of the study	External validity posed a special problem for students; it appeared that they need more research experience and better knowledge of the research field to address this issue.
References	According to the Vancouver style	This was the part of the proposal that tested students' eye for detail and a good practice for them in making a technically well-formatted report.

Table 2 (continued)

Proposal item*	What was expected from students	What students usually wrote in the first draft and how they revised it
Publication plan	Decision on the first-choice journal for the publication of results, indicate the web-page of the journal	Students liked this part of their proposal and often studied journals and their impact factors in detail. They also most often aimed too high.
Authorship	Provisional list of authors on the byline, according to initial work division. Planned contributions have to satisfy ICMJE† criteria.	This section provided the opportunity to discuss the difference between a thesis and a research paper. Students felt strongly about being the first authors inasmuch as they planed to make the largest contribution to research and writing.
Financing	Plan for or existing sources of funding	Usually no funding was planned or was available. This item was included to remind students about possible financial conflicts of interest and the need for their declaration.
Conflict of interest	Description of possible conflicts of interest	Usually none declared. This item was always discussed with a student, and they were asked to consult their mentors.
Intervention	Description of the intervention, if planned	Students rarely performed research involving testing of an intervention. This is the reason for putting this item so far in the proposal and making it optional. In rare instances of planned intervention studies, students needed assistance in clarifying the details about the intervention.
Preliminary research	Description of any pilot results, if they exist	Preliminary research was rarely performed by students. If they did a pilot study, they needed assistance in describing the result.

*Teachers read the proposal 1-3 times, providing suggestions what and how to correct and complete all items. Students also came for consultations and discussions on items they found difficult to address. Teachers insisted on technical and language excellence of writing.
†International Committee of Medical Journal Editors, www.ICMJE.org.

The Sixth Year

The sixth year was entirely devoted to the execution of research planned in the fifth year, including data collection, data analysis, interpretation and thesis writing. The final mark of the thesis was deduced from the sum of points the thesis was given for technical excellence (Supplementary table 2), average of points given by three members of the Graduation Thesis Defense Committee for the scientific quality of the thesis (Supplementary table 3), and average of points given by the three members of the Graduation Thesis Defense Committee for student's presentation and defense of the thesis (Supplementary table 4); 56% – 65% points was sufficient (grade 2), 66% – 75% good (grade 3), 76% – 85% very good (grade 4), and ≥86% points excellent (grade 5). The results of this year, i.e. the quality of the structure, content and style of the graduation theses surprised us. All students obtained, and deserved, excellent marks. We cannot assess how much this success was a product of our constant assistance to students, work of their individual mentors, clear-cut plans for research from the previous year's course, extensive instructions for thesis composition, detailed and transparent criteria of thesis evaluation and defense (Supplementary tables 2, 3 and 4), or of the maturation of students and their growing awareness that soon they will be headed to independent working positions. The experience was rewarding and highly appreciated by the students, their mentors and teachers at our Department, who provided methodological advice during the thesis work and writing. As in line with the University of Split regulations, the theses were made publicly available through the School's library webpage.

Discussion

As editors and educators we have found our work with students in teaching research

skills and scientific communication more rewarding than working with journal authors, who were already fully formed when they started being interested in research and publications (42). By the time most health professionals come to doctoral programs, which are the usual points of intervention for capacity building in research in developing countries (43), individuals are already formed and usually anxious about numbers, statistics and study design (44).

Medical students initially shared those anxieties but overcame them more easily and learned to appreciate the gradual increase in their own understanding and applicability of medical science, which in the end culminated with feelings of satisfaction and pride in the quality of their own research and diploma theses. Our analysis of students' responses to the course (and its 6 parts as shown in Table 2) was based on our communication with students (which was abundant), analysis meetings of the Department's members, reactions of mentors, and of students and members of defense committees at and after the defenses of the theses. The lack of an objective and systematic analysis thus opens the possibility that our evaluation was either biased or attributable to low evaluation criteria; however due to our familiarity with the previous thesis works, we believe we have substantially increased the criteria and evaluated them objectively. As the graduation theses made in the School of Medicine in Split are published on the internet (http://library.foi.hr/m3/ksrez.asp?B=419&N=50&V=FDI&J=&K=&O=&S=&css=&dlib=1&Upit=), those from years 2011 and 2012 are open to comparisons with those published before the new curriculum, as well as with those produced in other medical schools.

Finally, we truly feel there can be no good research for health if education for research does not come first (45). The research in biomedicine course, in all forms of knowledge and skills offered and required, empowers students of health professions to follow and practice principles of evidence-based medicine which no longer can be separated from everyday practice (42). Both searching for an answer to the question about a real patient and researching a novel intervention require careful definition of a question, identification and critical assessment of evidence and drawing relevant and objective conclusions. Teaching research needs to start earlier and be integrated with teaching practice. This is fully in line with the latest recommendations on basic medical education from the World Federation for Medical Education (Box 1).

Box 1. Recommendations of the World Federation for Medical Education (WFME) for science teaching in medical schools (Standards for basic medical education; The 2012 revision (ref. 20).

2.2. SCIENTIFIC METHOD
Basic standard:
The medical school **must**
- Throughout the curriculum teach
- The principles of scientific method, including analytical and critical thinking. (b 2.2.1)
- Medical research methods. (b 2.2.2)
- Evidence-based medicine. (B 2.2.3)

Quality development standard:
The medical school **should**
- In the curriculum include elements of original or advanced research. (Q 2.2.1)

Annotations:
- *To teach the principles of scientific method, medical research methods and evidence-based medicine* requires scientific competencies of teachers. This training would be a compulsory part of the curriculum and would include that medical students conduct or participate in minor research projects.
- *Elements of original or advanced research* would include obligatory or elective analytic and experimental studies, thereby fostering the ability to participate in the scientific development of medicine as professionals and colleagues.

For those willing to try a similar course schedule, we would recommend having students write their research proposals on the fourth year, and having "journal clubs" on the fifth, to enable students to discuss papers directly related to their own research topics. Even for those students who later in their careers decide not to partake in their own or others' research, we believe critical thinking they obtain through science teaching will forever remain an invaluable tool. It is now our further goal to cultivate a climate within our School and University which would enable publications of all students' work started as diploma thesis as full papers in peer-reviewed journals, and we therefore encourage other institutions to start building and strengthening research capacity from the first year of university level of health education.

Authors' contributions: Conception and design: AM, MM; Acquisition, analysis, and interpretation of data: AM, MMal, DS, AJ, MM; Drafting the article: AM, DS, MM; Revising it critically for important intellectual content: AJ, MMal.

Conflict of interest: The authors declare that they have no conflict of interest.

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Supplementary table 1

Principles of adult learning and course development*

Principles of adult learning
1. Education is best provided by individuals who have a deep understanding of their subject matter and whose teaching reflects that they care about and value the material being taught.
2. Educational programs should occur over an extended period; they should occur throughout a trainee's tenure.
3. Active participation in problem-oriented learning is an important component of effective educational programs.
4. Programs are more effective if educators help students assess their prior knowledge and integrate new material with familiar ideas.
5. Students should be encouraged to share their own experiences with others in the class.
6. Instructional programs that attend to developmental differences and individual learning preferences are more likely to be effective.
Principles of course development
1. Teach early skills in question recognition and formulation, searching, and critical appraisal, which should be taught and assessed as seriously as anatomy or pathology.
2. At the bedside, teach the application and integration of these basic skills, for example by giving students "educational prescriptions" – to formulate clinical questions and find answers before the next teaching session.
3. Teach students to explain evidence – about diagnosis, prognosis, treatment and their uncertainties – to patients.
4. Prepare students for the challenging task of integrating innovation and research into the realities of their clinics – by teaching them how to link evidence from systematic research with their personal experience and with patients' individual needs and hopes.
5. Since medical practice is open-book, to test and foster real world skills, all exams in all subjects should be open-book (except for some medical emergencies).

*Based on research reported in refs. 3, 23-33.

Supplementary table 2

Technical elements of student's graduation thesis evaluated by the teachers from the Department of Research in Biomedicine and Health

Thesis elements*
1. Technical presentation: Page breaks, indenting and line spacing, consistency of presentation through headings and subheadings.
2. Title: Clarity, congruence with hypothesis, indication of the type of study
3. Sample size calculation: Adequate description of sample size calculation, including formula details, data source, type of statistical test, study strength, P value and sample needed per group (if applicable).
4. Participants: Participants details, inclusion and exclusion criteria
5. Study groups: Study group(according to hypothesis), intervention and control group (if applicable)
6. Outcome measures: All outcome measures and their descriptors indicated (e.g. g/L, yes/no, etc.)
7. Confounding factors: Possible confounding factors listed, as well as their possible influence on the results
8. Ethical approval: Details of an approval by an ethical committee need to be listed, or the plan for its obtainment
9. Statistical analysis: All tests and programs used need to be listed
10. Language and style: Orthography, spelling, typing errors
11. Data presentation follows guidelines of the study used (e.g. STARD, STROBE, CONSORT)
12. Study flow diagram: Clarity, completeness, accuracy
13. Tables: Presentation, completeness, full title, clarity of the message, symbols used
14. Figures: Presentation, completeness of legend, clarity of the message
15. Referencing: ICMJE† style throughout the thesis

*Each element is given a score ranging from 0 till 2 (0 – poor, 1 – good, 2 – excellent). †International Committee of Medical Journal Editors, www.ICMJE.org.

Supplementary table 3

Scientific elements of student's graduation thesis evaluated by three members of Graduation Thesis Defense Committee

Thesis elements*
1. Title of the thesis: Congruence with hypothesis, clarity, type of study given and number of subjects/patients
2. Theoretical background of the investigation (Introduction): Logical stream („triangle"), clarity, relevance to the subject of research, logic of explanation for hypothesis/aim of the study, relevant citing
3. Hypothesis: Clarity, originality, importance
4. Appropriateness of the type of study: Are the type of the study and control group congruous with the hypothesis/aim of the study?
5. Sample: Did the author define a) population represented by the sample, b) type of sample, c) selection of subjects/ patients for the sample; laboratory animals or data sources?
6. Calculation of the minimal sample size: Is there clear-cut description of calculation, are all data included in the formula given, is the source/s of data for the formula given, which is the statistical test used, what are P-values, power of the study, and number of subjects per group (as calculated)?
7. Subjects/patients: Inclusion and exclusion criteria, experimental/test group (commensurate to the hypothesis), control group (commensurate to the experimental group)
8. 8. Outcome measures: Measuring units given for each listed outcome measure (e.g. g/L, yes/no, etc.), statistical measures specific for the type of the study (e.g. OR, RR, etc.)
9. Confounding variables and biases: Are the possible confounding variables and biases listed and how their influence on the results were controlled?
10. Statistics: All statistical measures of the outcome given, test applied for each analysis indicated, all *P*-values given
11. Flow chart of the study: Clarity, neatness, completeness, numbers in the boxes real and exact
12. Methods of data collection: Aources and methods of collection of all data listed, place of investigation, financing, appropriate ethical approval
13. Results – text: completeness and clarity of description of results, relevance of results to the hypothesis
14. Results – tables and figures: Each answers one question stemming from the deductive analysis of the hypothesis
15. Discussion: Logical flow („triangle"), soundness of explanation of scientific contribution, analysis of the weakness of the study
16. Conclusions: Clarity, originality, importance, foundation in the obtained results
17. Originality of research: With respect to the literature
18. Contribution to medical knowledge: At national and international level
19. Internal validity of research: Do the type of the study and outcome measures allow adequate testing of the hypothesis?
20. External validity of research: Generalizability of results discussed

*Each element is given a score ranging from 0 till 2 (0 – poor, 1 – good, 2 – excellent).

Supplementary table 4

Elements of student's presentation and defense of graduation thesis evaluated by three members of Graduation Thesis Defense Committee

Element	Points (from 0 – failure to 5 – excellent)		
	First member	Second member	Third member
Performance			
Quality of presentation slides			
Clarity of presentation			
Answers to questions of the Committee Member 1			
Answers to questions of the Committee Member 2			
Answers to questions of the Committee Member 3			
Total			

Review article

Acta Medica Academica 2014;43(1):63-68
DOI: 10.5644/ama2006-124.101

Importance of international networking in academic family medicine

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Received: 19 June 2013
Accepted: 22 October 2013

European family medicine/general practice (FM/GP) has travelled the long and successful journey of profiling the discipline and has produced valuable position papers on education and research. Nowadays, academic medicine is one of the pillars in the future development of FM/GP in Europe. A common European curriculum on undergraduate and postgraduate family medicine is needed. Also, a sound international platform of teaching institutions and/or teachers of family medicine would foster the further development of family medicine as an academic discipline. This would stimulate students and teachers to engage in international exchange to gain new knowledge and experiences, present their work and ideas abroad and prepare the conditions for further exchange of students and teachers**. Conclusion**. Established departments of FM/GP, led by a teacher who is a family physician/general practitioner, at each Medical School in Europe should provide students with knowledge and skills related to the core attributes of FM/GP. International exchanges of teachers and students should foster the development of a common curriculum on FM in Europe and foster improvement in the quality of FM education.

Key words: Family practice, Education, Network, Exchange.

Introduction

European family medicine/general practice (FM/GP) has travelled the long and successful journey of profiling the discipline (1) and has produced valuable position papers on education (2) and research (3). But the turmoil inherent to the medical field, with its subspecialisation and educational and research egoism has also shaken the field of academic family medicine. The European Academy of Teachers (EURACT), besides its Educational Agenda (2) has also developed criteria for the selection process, criteria for trainers and teaching institutions, which have been to a great extent incorporated into the curricula of specialist training in the majority of European countries (4) and are a framework for the continuing educational development of trainers in family medicine (5), but we still lack a common curriculum for undergraduate (6) and postgraduate studies in family medicine (7).

The exchange of students, because of the demands for a lengthy period of stay, is limited to those who are willing to stay abroad for one semester or more (8), but not for a few weeks, or as long as the teaching block in family medicine takes. Also, there is no common platform for exchanging university

teachers in Europe. These facts are the major obstacles for the further development of family medicine teaching and the discipline in general.

The aim of this article was to review the current situation in FM education in Europe and to present the possibilities of international networking.

Current situation

When looking behind the curtains of the podium disputes, we can identify three major risk factors for future stagnancy in the development of European FM/GP (9, 10):

1. The lack of common goals. This threat may be identified on the international level as the difference between countries in terms of size, health care system, position of FM/GP and the development of FM/GP (11). It is also seen inside individual countries, where everybody is busy with his/her own institution, organisation or a research project, but fails to recognise common goals. The multitude of family medicine textbooks in use also implies the lack of common goals (12).

2. Diversification of objectives. On the international level, one may observe this in the multitude of formal and informal networks and special interest groups (13) – all striving for justified individual FM/GP objectives, with little or no cohesion. This also happens within national contexts. Societies and colleges fight for the appropriate position of FM/GP within the national health services, emphasising the financial aspects and mandatory specialty training in FM/GP. On the other hand, university FM/GP teaching staff are busy working with students, protecting their own positions within the tough medical school environment and caring for their own staff. This leads to a lack of FM/GP representatives in national and international FM/GP bodies and organisations, which may negatively affect the position and development of the profession itself.

3. Asymmetric power distribution. The European Society of General Practice/Family medicine (WONCA Europe) is a large organisation, with an acceptable budget but few of its own large projects, relying mainly on networks and special interest groups, which sometimes pursue their own individual FM/GP goals, which are not necessarily always in line with the WONCA Europe mission. The Council seeks opportunities to diminish their differences by mixing the composition of the executive board, which cannot add much to their future development. Identical problems are found within individual countries, where in developed countries we can see a hidden or overt struggle between practitioners, professional organisations, regulatory bodies, universities, etc., and in less developed countries, the development of the academic science is usually overwhelmed in the struggle for financial recognition for FM/GP work.

Why is networking needed

The level of the "development" of the discipline in Europe is mainly measured through the successes of a few countries, thus putting the less well-developed and those not able to promote or adequately measure their development at the tail end of professional improvement of FM/GP in the world. This can lead to exposing the whole discipline to the risk that individual universities would try to squeeze out departments of FM/GP and replace them with more scientifically productive medical (sub)specialities, leading to even more sub-specialised curricula and less comprehensive and holistic education (4). We have to take into account that, in the absence of a clear position of the FM/GP profession regarding the content and objectives of FM/GP teaching in medical schools, heads of departments are sometimes not experts in FM/GP but they come from other disciplines (14). As such, they are usually

under pressure from the Dean, who usually compares his own faculty with other faculties. This can result in the situation where FM/GP in that university is not in an optimal position. A formal position statement accepted by WONCA would improve the situation on this issue (10).

Moreover, the first two strategic goals published on the official WONCA Europe website (15), i.e.: 1) Mandatory undergraduate education in FM/GP at all medical schools in Europe and 2) Academic departments of FM/GP at all university medical schools in Europe, still have to be accomplished at many European Universities (16). We can claim that FM/GP in Europe may become a victim of its own success. In the nineteen-seventies, we had a common goal with a few objectives. However, the developments in the nineties brought us to the point where some countries enjoyed a victorious position and others just saw a reflection of their aims (through these countries). Finally, the new millennium brought changes to all of us (10). The position of FM/GP is under heavy debate and financial pressure, mainly from the health authorities. To turn threats into opportunities, we need to establish a sound platform to aid the sustainability of teaching activities in the future.

Possibilities of international networking

A broad project consortium of experienced partners/teachers from all over Europe, together with the involvement of the two WONCA Europe existing networks, especially EURACT, that includes representation of 41 European countries, with over 800 direct members, would assure that the network for FM/GP academic collaboration in Europe will be sustainable for longer. Its objectives could include several items (Box 1) (10).

Box 1:

1. Promotion of common family medicine content and context in Medical Schools' curricula (17).
2. Networking and collaboration in the field of basic medical education.
3. Platform for the exchange of curricula, programmes, projects in undergraduate and postgraduate education.
4. Network for student and teacher exchanges (8).
5. Collaboration with other WONCA networks, special interest groups (SIGs) and different regional networks.
6. Teaching agenda for undergraduate education (17).
7. Quality improvement of undergraduate and postgraduate teaching (7).
8. Teaching teachers' courses.
9. Research in postgraduate education.
10. Innovative approaches in undergraduate teaching (18, 19).
11. Support to less developed departments/medical schools.
12. Core family medicine curricula for basic medical education (17).

Good examples from family practice specialization training development could serve as a benchmark in these processes (2, 20). An example of successful collaboration is the assistance for family practice training development in Montenegro, where foreign experts helped to introduce an improved curriculum of family medicine (21).

Practical examples of successful networking

The Department of Family Medicine of the Maribor Medical School (22) and the Department of Family Medicine from Zagreb Medical School have a long tradition in the international exchange of students and teachers. It started in the 2007/2008 academic year when students and teachers from Maribor arrived in Zagreb for a one-day study visit, presenting curricula and student assignments. Until December 2012, these exchange visits were bilateral. On the last exchange visit, the Department of Family Medicine from Ljubljana Medical School joined us.

Table 1 Aims of exchange visits for students and teachers

Aim	Students	Teachers
Learning about foreign medical schools.		
Learning about different education systems and education methods.		
Exchange of problems and mutual solution seeking.		
Opportunity for presenting one's own work to others.		
Preparing settings for the further exchange of students and teachers also for longer periods of time.		
Gaining new knowledge and experiences.		
Improving public speaking and presentation skills.		
Seeking ideas for common projects.		

Table 2 Networking in Maribor Department of Family Medicine

City of networking	Belgrade	Graz	Ljubljana	Podgorica	Sarajevo	Skopje	Zagreb
Type of co-operation	Teachers' exchange	Teachers' exchange	Exchange of teachers, students and researchers	Teachers' exchange	Teachers' exchange	Teachers' exchange	Exchange of teachers, students and researchers
Project/s	Visiting professorship	Visiting lectures	Research projects	Visiting lectures, trainees' assessment	Visiting lectures	Visiting lectures, trainees' assessment	Students' conferences, teachers' conferences, research projects
Content	Lectures	Lectures	Research	Lectures, assessment	Lectures	Lectures, assessment	Presentation of student research and seminar work, presentation of teaching methods
Aim	Support for family medicine teaching in undergraduate education, support family medicine teaching in specialty training	Support for family medicine department development	Develop high quality research	Support for family medicine department development	Support for family medicine department development	Support for family medicine department development	Support for students in family medicine topics, support to improve teaching methods, support in research and publishing
Benefits	Students have access to high quality lectures, Trainees have the opportunity to listen to teachers from abroad	Members of family medicine departments get support in their endeavours to establish a chair	Joint research, better ranking of research group	Trainees have access to high quality lectures, calibration of assessment criteria	Building collaborative attitudes	Trainees have access to high quality lectures, calibration of assessment criteria	Students learn about each other's achievements, teachers have the opportunity to compare their teaching methods
Comment	High level of support from the family medicine department chair and leadership of the medical school	Support of the dean of the medical school	High level of support from the family medicine department chair	High level of support from the family medicine department chair and leadership of the medical school	High level of support from the family medicine department chair	High level of support from the family medicine department chair and leadership of the medical school	Long tradition of cooperation and mutual support

These one-day exchange visits consist of both formal and informal parts. During the formal part, selected teachers from all participating medical schools present their teaching methods, their teaching achievements or their developments as teachers. This is followed by presentations by the students, which includes presentations of their seminar works and/or their research projects. The formal part of the programme ends with a discussion, usually in mixed groups. The topics concentrate on learning about good practices/achievements in the study process and also what may be improved and how to achieve this. In the informal part of the study visit, the host students show the visitor students their faculty and their living situation. Meanwhile, the teachers engage in informal conversations about the teaching process, their experiences etc. The aims of such exchange visits are shared by students and teachers (Table 1).

One of EURACT's aims is fostering the exchange of experiences among its members in order to improve patient care in the member states. The exchange is conducted mainly by study visits of teachers to universities and conferences, and it is very vibrant in South Eastern Europe (23). Table 2 provides some examples of networking by the Department of Family Medicine of the Maribor Medical School.

Conclusions

Academic medicine is one of the pillars of the future development of FM/GP in Europe. Established departments of FM/GP led by a teacher who is a family physician/general practitioner at each Medical School in Europe should provide students with knowledge and skills related to the core attributes of FM/GP. Teacher and student exchanges are able to contribute to the development of common curricula. A network of University FM/GP departments would facilitate such developments.

Authors' contributions: Conception and design: JK; Acquisition, analysis and interpretation of data: JK, ZKK; Drafting the article JK; Revising it critically for important intellectual content: ZKK.

Conflict of interest: The authors declare that they have no conflict of interest.

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Review article

Acta Medica Academica 2014;43(1):69-75
DOI: 10.5644/ama2006-124.102

Academic cooperation in family medicine: A viewpoint from Split

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Received: 24 June 2013
Accepted: 19 December 2013

The problems, current status, and opportunities of national and international collaboration between the academic family medicine institutions in Southern Europe, particularly in the region of ex Yugoslavia, as perceived from the standpoint of the Department of Family Medicine in Split University School of Medicine, Split, Croatia, are presented in this brief review. A historical survey of this department's educational, professional, and scientific development from its establishment in 1997 is given to place the regional issues in context. Family physicians are strong in number here – around 53 family practitioners per 100,000 inhabitants in Croatia, similar to surrounding countries, but weak in academic representation, with only 18 active faculty members. This compares to general internal medicine with 28 practitioners per 100,000 inhabitants and 106 active faculty members. The reasons for such a disproportion are analyzed, and the importance of collaboration is stressed. **Conclusion**. Although there have been several cooperative efforts, these activities can and should be intensified. While there is much work to be done, there are many opportunities for improvement.

Key words: Academic medicine, Cooperation, Family medicine.

Introduction

More than a century has elapsed since Abraham Flexner, a renowned educator and descendant from a physicians' family, radically influenced the concept and structure of medical education with his report on the poor condition of medical schools in North America (1). The basic tenets of a good medical school, which had to incorporate not just teaching, but also a trinity of scientific investigation, health services, and education of future medical professionals, were set. This approach marked a turning point in the concept of medical education worldwide. These principles apply to all components of a medical school, including family medicine (FM).

As a professional league, FM is very numerous (for instance, in Croatia, with about 4.4 million inhabitants, there are 2,345 family physicians or a ratio of about 1:1900 inhabitants), while as an academic discipline it is tiny and understaffed. Indeed, four FM chairs in this country have just 18 faculty members (9 professors and 9 associate professors). Although FM is the most numerous in terms of practitioners, its educators are few and far between. By comparison there are 1225 general internists and 248 of them are faculty members (with 57 professors and

49 associate professors).This disproportion may be due to several factors. In particular there is a negative selection; hospital residencies are preferred, and FM specialization is not mandatory for FM practice in Croatia. Consequently, a number of FM practitioners in Croatia are not specialist/consultants in the field (1151 out of 2345 or 49.1%) and are therefore practically banned from scholarship/faculty election. Moreover, current capitation, a counterproductive way of financing primary care, stimulates agglomeration of health care beneficiaries (patients) with decreasing quality of care due to lack of time and space. All that may be summarized in two opposite trends: shortage (in motivation, proficiency, scholarship, practice-academia interaction) and surplus (in overbooked visits, administrative, financial and organizational burdens, isolation, and substandard office equipment). Nevertheless, a study across Croatia has shown that FM practitioners have a highly affirmative attitude towards medical science (about 80% gave very positive answers) and scientific/professional literature (over 90%). However, their publication activity was low (papers referred to in Index Medicus have authored 6%, and in Current Contents just 1.6% of them) (2). As academic involvement is a mainstay of publication, increasing of this process to match FM support of scholarly activity will necessarily involve research and scientific education.

The aim of this short review is to present the current status of cooperation between the academic departments of Family Medicine in the region as seen at the Split department, and to outline opportunities for improvement.

Department of Family medicine in Split University School of Medicine

The Split chair of family medicine sprouted from the Zagreb alma mater in 1976, and became an independent department in 1997 with the establishment of the Split University School of Medicine, the first graduate school founded in the independent Republic of Croatia. It has a peculiar undergraduate curriculum of 180 teaching hours per student (100 hours of practice, particularly on the islands and in the rural areas of the Dalmatian Highland consisting of autonomous work under tutorial supervision; 60 hours of seminars with case presentations or role playing; and 20 hours of interactive lecturing).

At the time of its constitution, the Split department of FM consisted of only one associate professor and six assistants, three of them with a MB degree, and some 20 practice tutors (their number varied according to the number of enrolled students, since each tutor/mentor could accept no more than two of them in the office). Summative exams were composite from the beginning (a multiple choice written test, patient consultation in the tutor's office, and oral examinations with pulling of announced questions). Our parent chair and its staff from Zagreb was initially of invaluable help in the teaching process and in the summative students' assessments.

After some years, a visiting professor in FM from the Ljubljana School of Medicine (Slovenia) was elected in 2007 (3) and continues to lecture here today. The teaching subjects and contents were permanently accommodated to current practice issues (e.g. controversies in the management of hyperlipidemia or diabetes mellitus type 2) or sociomedical problems (e.g. patients' rights, family violence, bullying). The freshmen, in their first study year, were already exposed to the FM perspective within the subject "Introduction to medicine" (25 hours, since 1997). Student polls consistently rated this course as highly appreciated. Unfortunately, the subject was truncated in 2009. Some improvements have been incorporated in the FM curriculum, particularly in the summa-

tive part of the FM examination, since the tutorial assessment was not reliable enough; instead of this, OSCE (Objective Structured Clinical Examination) was introduced in 2010. For its sake a practicum of clinical skills was published in 2012 (4). Several dolls and models for OSCE were borrowed from the Mostar University School of Medicine since its FM department introduced this kind of practical examination in 2009. In addition, as a part of the exam letters to the patient (5) and PEARLS (Practical Evidence About Real Life Situations and/or Presenting Evidence Abstracted from the Research Literature for the Solution of real patient's problems) were introduced (6).

Scientific advancement and scholarly achievements were occurring at a much slower pace, presumably due to the age of the assistants (mean around 48 years) and the just started, detrimental FM privatization/leasing (from 1998; formerly all FM practitioners were community health center employees), which forced doctors to devote time to business practice instead of medicine. The department has slowly rejuvenated over the past ten years, first with the admission of two assistants (one with the MB degree), and later with two novices on the international INTER HEART 2 project, animating scientific publication, thesis and dissertation defense, and scholarly progress (3). Today the Department has one professor, two associate professors, three PhDs, two senior lecturers, five assistants, and six practice tutors (the number of the latter is variable, according to the number of enrolled students).

International and interfaculty cooperation

This collaboration, both at the national and international level, depends on mutuality in the fields of scientific endeavor, patient care services, and education of future doctors (Table 1).

The opportunities at the international level, e.g. EGPRN (European General Practice Research Network), EURACT (European Academy of Teachers in General Practice) or WONCA Europe, are underutilized. Regional interdepartmental synergy remains low (Figure 1).

The Slovenian chairs from Ljubljana and Maribor are unique, having developed successful interaction not only with Croatia, but also with Bosnia and Herzegovina, Macedonia, Montenegro, and Serbia (7, 8).

Our department has established good links with Bosnia and Herzegovina (mostly with Mostar, less with Sarajevo) in terms of

Table 1 Opportunities for interfaculty cooperation

Science	Education		Profession
	Undergraduate	Postgraduate	
Coordinated research projects (e.g. within EGPRN)	Preparing joint textbooks; curricula fostering; EURACT cooperation	CME courses; EURACT	Congresses and other conventions (e.g. WONCA Europe, HOUM*)
Scientific papers, co-authorship	Exchange of teachers and programs (e.g. visiting professorship)	Teaching courses; seminars for medical educators	Permanent exchange of visits and ideas
Mentoring, coaching young researchers	Student exchange (e.g. Erasmus, practice groups)	Targeted meetings (e.g. DNOOM**)	Mutual evaluation of new technologies
Joint scientific boards, guideline committees	Reciprocation in teaching aids and summative assessment techniques	Harmonization of curricula	Synchronized legislative proposals

*HUOM: Croatian Society of Family Medicine; **DNOOM: Association of Teachers in General and Family Medicine.

Figure 1 Bidirectional arrows on the chart show the actual interfaculty cooperation in this part of Southern Europe. Thicker arrows indicate higher intensity of collaboration. Links between Zagreb (Croatia), Maribor and Ljubljana (Slovenia) with Skopje (Macedonia) are not shown for graphic reasons.

lecturing, summative exams, coaching/mentoring of term papers (MB, PhD theses), and continues its relationships with Zagreb and Ljubljana.

Slovenian colleagues, in addition to one visiting professor, have contributed with their authorship to our recent FM textbook (9).

Although most departments are deeply interested in collaboration, at least declaratively, it is seldom materialized in practice, and when implemented it is often in a unidirectional way.

Some efforts towards international cooperation have been done. In particular the chairs in Maribor, Mostar, Ljubljana, Zagreb, and Split are striving to invigorate these relationships. Cooperation must be a two-way street, i.e. mutual: all the participants must profit. Currently, there are several obstacles on this path, such as inadequate infrastructure, geographic remoteness, an unfavorable economic situation in some regions with repercussions on their medical schools, and understaffed academic departments. Synergy between our chairs in these circumstances can not be perfectly balanced and bidirectional; it is understandable and almost mandatory that "stronger" chairs help the "weaker" ones until their material base and scholarship matures (examples are Zagreb – Split, Split – Mostar, and Ljubljana – Podgorica, Montenegro). Nevertheless, the departments in Ljubljana and Zagreb are currently preparing a common FM textbook.

As an academic discipline we are not flamboyant; individually we are weak, even

at the level of our medical schools by virtue of our low numbers in academia. United we may instigate a number of relevant, multicentric, and complementary clinical studies, promote academic achievements of our colleagues, and enhance the appropriateness and efficiency of primary health care. Publication in peer reviewed journals must also be stimulated, including the local periodicals (e.g. Medicina Familiaris Croatica is regularly published since 1992, with two issues per year).

The study of medicine has recently regained its appeal, and the number of young people eager to become doctors is anticipated to increase, especially in our region, which will expand the need for medical teachers (moreover, there are studies in English at Zagreb and Split Medical Schools). The emphasis on health care, not only in the region but worldwide, is moving from hospital and specialist towards primary care and family medicine because it is more effective, less expensive, and hence more sustainable (10). Especially important are the issues of primary care management and comprehensive approach; person-centered care, holistic approach and community orientation are the future of medicine and the province of FM.

Conclusion

We recommend the following specifics to achieve our goals:

1. **Scientific research**. Focus on clinical and epidemiological studies, particularly concerning quality of life and preventive activities, aimed at clinically relevant outcomes (PCOR, i.e. Patient-Centered Outcomes Research) (11). These can be done at the student level as part of their core curriculum, and can be supported by practitioners mentoring these students. Consider formally studying the following current issues within our community, all easily investigated within our patient population:

- effectiveness and risk/benefit evaluation of prescribing allopurinol vs. placebo to asymptomatic hyperuricemic patients (acute attacks, tophi, atherosclerotic, especially coronary heart disease) (12); effects of vitamin C (13), cherries (14), and their combination on uric acid levels and incidence of acute gouty attacks;
- clinical effectiveness of chondroitin sulphate, glucosamine, their combination, or placebo on knee osteoarthritis managed with the optimal standard therapy (15);
- impact of PSA screening for prostate cancer in primary care on the survival of male middle-aged patients (16);
- effectiveness of antibiotic treatment (amoxicillin + clavulanic acid) for patients with low back pain lasting over 6 months (17).

2. **Medical education**. Continue to improve and harmonize the undergraduate and postgraduate teaching process (18, 19) in cooperation with international FM organizations, such as the mentioned EURACT in Europe or STFM (Society of Teachers of Family Medicine) in the USA. Consider the following attempts:

- exchange of experience with the existing and/or novel teaching aids; weighing the reasons for and against their routine implementation;
- balancing and updating the catalogues of skills, knowledge, and attitudes sought and taught within our medical schools;
- improving specific problem solving competency through formal study of how to solve clinical problems and testing these skills in an OSCE environment (e.g. decision making skills, management of comorbidity/multimorbidity);
- coordination of examination criteria for undergraduate and postgraduate studies; comparison of the existing summative assessment programs (Table 2).

Table 2 Scoring at the undergraduate FM examination in Split, academic year 2012/13

Contents	Possible score
Written part (MCQ)	0-30 points (passing threshold ≥18)
OSCE	0-25 points (passing threshold ≥16)
Verbal part	0-45 (passing threshold ≥27)

FM=Family Medicine; MCQ=Multiple Choice Questions; OSCE=Objective Structured Clinical Examination; theoretical range 0-100 points; cumulative passing threshold: 60 points. PEARLS and letters to patients are mandatory for exam admission but not rated.

3. **Professional issues**. Improvement in competencies and social rating of family physicians (6, 18). In particular improving the perception of FM by other specialists by:

- setting FM guidelines for some imaging (e.g. CT or MR) referrals or for the prescription of some outpatient medications, which are mainly relegated to a narrow spectrum of specialists or subspecialists with no clear scientific, economic or professional grounds;
- harmonization of guidelines for referral to consultant specialists;
- proposing the minimal equipment for a FM office (e.g. minor surgery set, otoscope etc.), indicating the desirable equipment (e.g. ultrasound, ECG etc.), and stressing the needless ones (e.g. bone densitometer, x-rays machine etc.).

Working together we have the ability to overcome our challenges and improve outcomes for our patients, while increasing interest in FM and improving the quality of our practices.

Authors' contributions: Conception and design: MR,DP; Acquisition, analysis and interpretation of data: MR, DP; Drafting the article: MR; Revising it critically for important intellectual content: MR, DP.

Conflict of interest: The authors declare that they have no conflict of interest.

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Short communication

Acta Medica Academica 2014;43(1):76-80
DOI: 10.5644/ama2006-124.103

Academic model of trauma healing in post-war societies

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Received: 30 September 2013
Accepted: 16 January 2014

Objective. The aim of this paper is to examine the implications for healing in a contemporary Balkan post-war context, and to provide a bridge-building model of trauma transformation, reconciliation and recovery through academic reconstruction and cross-border dialogue. Post-war societies are marked by the effects of massive, large group traumatization, and if not properly dealt with, long-term rehabilitation and social recovery cannot be expected. Unprocessed cumulative trauma that has become deeply embedded in the collective memory of the Balkan peoples over centuries, „chosen trauma", its trans-generational transmission and periodical reactivations across the Balkan have often been addressed in recent literature, in ethno-psychology, psychoanalysis, psychiatry, sociology and anthropology. In order to deepen our understanding of the roots of collective (social) trauma and the specific traumatic experiences of different groups, and to offer different perspectives and information on how trauma can be dealt with, the "Trauma Trust Memory" multinational interdisciplinary research network is being established, and a groundbreaking workshop was held in May 2013 in Tuzla, Bosnia-Herzegovina. **Conclusion.** The Tuzla Workshop showed that the active participation of affected groups in adequate coping with the past is required for post-conflict reconstruction, trauma healing and peacebuilding in the long run.

Key words: Post-war societies, Trauma healing, Academic reconstruction.

Introduction

The dissolution of the ex-Yugoslavia in the early 1990's was followed by the Slovenian, Croatian and Bosnia and Herzegovinian (BH) declarations of independence, which resulted in war (1991-1999) characterized by war crimes, crimes against humanity and genocide (1-3). Survivors report mass destruction, the prominence of ethno-nationalism, wide-scale violation of human rights, ethnic and political persecution, forced mi-

grations, enslavement, concentration camps, mistreatment of prisoners, starvation, murder of the civilian population, mass rape, executions, and mass graves (1-4).

The wars in ex-Yugoslavia had dramatic consequences for all the republics of the former Yugoslavia, and more specifically BH, where the most hostile actions and violent battles took place (3-4). The final figures on the horrendous atrocities committed during the war (1992-1995) in BH (1-4): 103,000 killed, of which 60% civilians, 30,000 missing persons, 170,000 wounded, over 20,000 raped, and over 2 million became refugees or displaced persons, most of them driven from their homes in pogroms of "ethnic cleansing".

With the aim of overcoming individual and social experiences of traumatization and to create the conditions for subjective and collective reconciliation and healing, through academic reconstruction and collaboration, a Stability Pact based the multinational research network – "Trauma, Trust and Memory" (TTM) - was founded in January 2013, in partnership with the German Academic Exchange Service (DAAD), connecting the interdisciplinary work of the International Psychoanalytic University (IPU) in Berlin to research centers on social trauma in BH, Bulgaria, and Serbia. The transfer between clinical and cultural scientific expertise - through psychotherapy research, epidemiological studies, psychological studies of trauma experience and processing, studies on the cultural processing of collective trauma through literature and film analyses - is a specific feature of the TTM Network. The terms "academic-oriented trauma healing" and "academic reconstruction" are used in this paper. We define academic–oriented trauma healing as the process in which explanatory models of complex trauma processes and trauma effects on the next generation, as well as trans-generational trauma healing, should be developed through trauma research and facilitating discussion about trauma consequences, within multinational interdisciplinary groups of students, professors and practitioners. This paper uses the term academic reconstruction within the framework of the DAAD/TTM network program referring to: a) improving the quality of education and training in the field of social trauma offered at institutions of higher education in South Eastern Europe (SEE); b) establishing a teaching and research inter-institutional network with the aim of fostering cross-border co-operation; c) targeting support for young academically qualified experts from the region, while initiating joint research projects. Apart from the academic exchange of direct beneficiaries of this program (the network members and institutions), the students, lecturers and practitioners are motivated to share their knowledge and experience by taking part in a wide range of activities related to trauma transformation, reconciliation and peacebulding through local community outreach projects.

Academic-oriented Trauma Healing – Our experience

A social trauma is the consequence of traumatic events (i.e. war), which develop within the context of one's own group or community. Post-war societies in the Balkans are marked by the effects of massive large group traumatization that is multidimensional, and therefore we use an interdisciplinary approach to trauma healing. Our aim is to face history, and to make traumatic traces visible and addressable. We enhance dialogues on social trauma between psychiatry and psychoanalysis, psychology and history, clinical, conceptual, empirical qualitative and quantitative approaches, academic and therapeutic contexts as well as survivors' organizations, from different countries looking back to a long history full of atrocities.

We come from different cultures, but we share similar aspirations, being inclined to a thorough understanding instead of quick judgments, to dialogue instead of quarrel, and to reflection instead of projection. If trauma causes the disintegration of linking processes within the psyche, such that overwhelming traumatic experiences cannot be integrated into an affect-connected long-time memory, but circulate like errant fighters in the jungle of a fragmented autobiography – then what helps is acknowledgement, respect, and connection by naming the truth. In our social histories there are also many fragmented discourses. The borders we are crossing through our network may be characterized by pointing to the history that marked some of us in the early nineties: the Yugoslav wars and the overthrowing of the Socialist Systems. The experiences, such as dictatorship, torture, war, rupture within families and neighborhoods, genocide, ethnic cleansing and mass rapes that took place in this region not so long ago are to be shared – the survivors are still alive and young, and some of the researchers connected in this cooperation are able to tell a personal story. The historical lines that cross here are highly interconnected with each other and with European, and especially German history. The network comprises research into the traumatic impact of dictatorial societies and war, be it in clinical or cultural studies. In the first six months of our joint work, the thematic and methodological fields of cooperation were identified and developed in workshops, fellow-trainings, and summer schools. In May 2013, a groundbreaking Workshop entitled: "Social Trauma, Trust and Collective Memory" on Complex Trauma, Group Identity and Reconciliation, was held in Tuzla, BH. The Workshop aimed at providing an overview of current trends in the areas of the complexity of adolescent and social trauma with its aftermath, and research and clinical practice in post-conflict countries, with the contribution of prominent experts in various fields. A keynote lecture on *Complex Traumatization in Adolescents* and a presentation about the ways in which social trauma caused extreme attitudes among young people in East Germany was given by the child and adolescent psychiatrist and psychoanalyst, Professor Annette Streeck-Fischer from IPU Berlin, now President of the International Society for Adolescent Psychiatry (ISAP). Various clinical illustrative presentations were given throughout the workshop.

Since the workshop schedule coincided with the 18th Anniversary of the „Massacre of Tuzla Youth", a documentary „Tonight, we will love for them" was presented in the workshop session *Facing the Past - Transforming our Future.* After that the participants remembered the victims at the Kapija Memorial. Also, the participants visited the association helping the victims and survivors of sexualized violence in war, "Our Voice," and the association for mutual assistance in mental distress "Fenix", to learn more about the importance of psychosocial intervention and social support for users' associations. On the last day of the workshop, within a session entitled *We Can Make a Difference,* the group visited the Srebrenica-Potocari Memorial and Cemetery for the Victims of the 1995 Genocide and paid tribute to the victims.

Presentations on "Group Identity and Reconciliation", "The Practical Application of Contact Theory in BH", and "The Link between Trauma, Conflict and Sustainable Peacebuilding" stimulated group discussions, where we collectively addressed the challenges of applying the "Trauma, Trust, and Memory" network, while facing the „traumatic traces of our history." In trying to understand better the roots of social trauma and the consequences of mass atrocities, we tackled the topics of large social group identity, narcissism of small differences, "chosen

trauma", the phantasm of revenge, victim playing as a coping strategy, trans-generational trauma transmission, false history, and the "conspiracy of silence" around these issues (5-7). The workshop was thoroughly interactive, initiating science dialogue that spontaneously illustrated the beginning of trauma-transformation and peace building efforts focussing on building relationships and trust across the borders, which in our recent past represented conflict lines.

Future directions

In BH today, where we are still facing the continual fabrication of ethno-nationalism, the wide-spread denial of atrocities and impunity, initiating trauma transformation, the repair and restoration of relationships, rebuilding trust and strengthening reconciliation in a tense post-conflict arena is difficult, but hope-infusing and promising. From the perspective of our local contexts and situations, the TTM Workshop in Tuzla provided a real opportunity to transcend boundaries and build a learning collaborative of people from the academic societies of different countries in the region, who can work together to provide the cross-border cross-sector collaboration needed to support the achievement of the TTM Network objectives. It is not only a scientific exchange, but also the personal and the political bridges that are built through this cooperation. And, as we know from the feminist academic debates back in the sixties (8), "the personal is political" – since it has to do with human beings, even if it does not always seem so – and in reverse, the political is personal, since we live and grow in contexts. We can do something to improve them. Our working alliance in the TTM network is but one step. The Tuzla Workshop resulted in a wide spirit of collaboration and determination to continue the dialogue, especially among young scientists, researchers, and clinicians. This will hopefully form part of a joint academic reconstruction project, which draws upon regional perspectives to deepen understanding of social trauma, reduce mistrust, and facilitate reconciliation and healing. Serving as a platform, where science, therapeutic and teaching practices, dialogue and empathy come together in healing the wounds of history, the DAAD supported "Trauma Trust Memory" project aroused and encouraged interest in cooperation and/or coordination of efforts with other academic sectors and agencies working in different areas: i.e., history, sociology, peacebuilding, journalism, and maintaining survivor organizations. This should magnify the impact for a broader peace, aiming at producing and strengthening significant personal transformations in attitudes, perception and trust, and translating these personal transformations into actions at the socio-political level (9).

Conclusion

Enhancing the "Trauma Trust Memory" research network, continual interdisciplinary networking, collaboration and friendship through high-level academic dialogue, training workshops, study visits and joint projects, should be a must in any future strategy of academic reconstruction and developments in post-conflict societies in the Balkans, and not only in the Balkans.

Authors' contributions: Conception and design: Am.D MH, Al.D, AH; Drafting the article Am.D, MH, EA, Al.D, AH; Revising it critically for important intellectual content: Am.D, MH, EA, Al.D, AH, CH, CS, TSS, ASF.

Conflict of interest: The authors declare that they have no conflict of interest.

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Short communication

Acta Medica Academica 2014;43(1):81-86
DOI: 10.5644/ama2006-124.104

Research projects in family medicine funded by the European Union

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Received: 19 November 2013
Accepted: 12 March 2014

Objective. This study aimed at synthesizing funding opportunities in the field of family medicine by determining the number of family medicine projects, as well as number of project leaderships and/or participations by each country. This was done in order to encourage inclusion of physicians in countries with underdeveloped research networks in successful research networks or to encourage them to form new ones. **Methods.** We searched the Community Research and Development Information Service project database in February 2013. Study covered the period from years 1992 – 2012, selecting the projects within the field of general/family medicine. The search was conducted in February 2013. **Results.** First search conducted in the CORDIS database came up with a total of 466 projects. After excluding 241 projects with insufficient data, we analysed 225 remaining projects; out of those, 22 (9.8%) were in the field of family medicine and 203 (90.2%) were from other fields of medicine. Sorted by the number of projects per country, Dutch institutions had the highest involvement in family medicine projects and were partners or coordinators in 18 out of 22 selected projects (81.8%), followed by British institutions with 15 (68.8%), and Spanish with 10 projects (45.5%). Croatia was a partner in a single FP7 Health project. **Conclusion.** Research projects in family medicine funded by the European Union show significant differences between countries. Constant and high-quality international cooperation in family medicine is the prerequisite for improvement and development of scientific research and the profession.

Key words: International projects, Project database, Family medicine, Cooperation.

Introduction

The European Union funding of research projects includes funding opportunities available through Lifelong Learning Program (LLP), 7 cycles of Framework Program (FP), and projects within the framework of Instrument for Pre-Accession Assistance (IPA) (1, 2). Framework Programs have been in existence since 1984, and have so far completed seven cycles (3). The Seventh Framework Program was active for seven years, since January 1st 2007, until the end of 2013. The goal of the FP7 projects Health group was to improve the health of European citizens and focus on solving global health problems. It encouraged collaborative research, with the objective of establishing excellent research projects and networks able to attract researchers and investments from

Europe and the entire world. Programs from this trans-national collaborative research encouraged development and validation of new therapies, methods of health promotion and disease prevention, including promoting health of children, healthy aging, diagnostic tools and medicinal technologies, as well as efficient and sustainable health care systems. However, family medicine as a subset of health care in general was one of the least-funded fields, indicating the need for increased funding in the future.

Although research in family medicine in the Republic of Croatia has a longlasting tradition (4), a sustainable research network does not yet exist. There are many reasons for this, but the main ones related to the topic of this study are the inadequate national funding reserved for this field, lack of continuity, as well as an insufficient number of quality researchers. So far there have not been enough quality studies conducted in the field of family medicine in Croatia (4). Receiving additional opportunities to access the EU funding would greatly help in addressing all of these three issues. The chances for accessing the EU funding will hopefully be greatly improved by the recent (2013) joining of Croatia to the EU.

The aim of this study was to provide synthesis of funding opportunities in the field of family medicine by determining the number of EU funded projects in family medicine, their number and project leaders by country, and number of institutions from that country were included in these projects in order to encourage inclusion of physicians in countries with underdeveloped research networks in successful research networks or to encourage them to form new ones. This might influence further choices of project partners (whether it is high-achieving countries' institutions reaching out to those just starting out, or vice versa) when assembling teams for future projects, as well as the future allocation of funds by policy-makers. It should also provide any neutral observers with a quick snapshot of the current state within the field of family medicine reasearch.

Methods

The CORDIS (Community Research and Development Information Service) project database includes all public information (project factsheets, publishable reports and deliverables), editorial content communication and exploitation and comprehensive links to external sources such as open access publications and websites. We independently searched the CORDIS project database for the EU funded projects available in the database for the period from 1998 to 2012 using the following keywords: family medicine, general practice, family medicine health care, and primary health care. For the purpose of this article, we defined family medicine in the European area as a subset of primary health care, which involves a comprehensive and holistic provision of preventive, diagnostic and health treatment services to all patients in the practicioner's community.

All projects that did not have available data on project type and duration, the state coordinator of the project and the participating countries were excluded. We analysed abstracts of all remaining projects, and selected those within the field of general/family medicine for further analysis. Due to the number of eligible projects containing all the required data being very low, we expanded the search to the period of 1992-2012 and repeated this process. All disagreements have been resolved by discussion and consensus.

Results

First search conducted in the CORDIS database came up with a total of 466 projects. After excluding 241 projects with insufficient data, we analysed 225 remaining proj-

ects and found that out of those, 22 (9.8%) were in the field of family medicine and 203 (90.2%) were from other fields of medicine. Of those 22 projects in the field of family medicine, 11 were FP7 projects, 2 FP6, 5 FP5, and 1 each from the following groups: Leonardo da Vinci (1995-1999), Peco/Copernicus (1992-1994), STD 3 (1992-1995) and AIM 2 (1990-1994). The FP7 cycle is further divided into specific programmes. Out of 11 FP7 projects, 10 were funded within the specific programme "Cooperation", and 1 project was funded within the specific programme "Ideas".

When sorted by the number of projects per country, Dutch institutions had the highest level of involvement in family medicine projects and were partners and/or coordinators in 18 out of 22 projects examined (81.8%), followed by British institutions with 15 projects (68.8%), and Spanish with 10 projects (45.5%) (Table 1).

Dutch researchers coordinated 8 (36.36%) projects, and were partners in 15 (68.18%) projects. The highest number of institutions included in a single project (n=38) cooperated in the project „The care and management of services for older people in Europe network", which also included the highest number of institutions per country (n=3.8) (Table 2). Other than 19 countries with a medium level of involvement, there are also

Table 1 Participation of European countries* in family medicine projects (n=22) financed through FP7†, FP6‡, FP5§, LEONARDO DA VINCI, PECO/COPERNICUS, STD3‖ and IM2¶ programs, sorted by number of project leaderships **for each country

Country	Number of projects			
	By country	Leaderships	Participations	Institutions
Netherlands	18	8	15	36
United Kingdom	15	4	13	38
Denmark	7	2	7	10
Spain	10	1	11	17
Sweden	9	1	7	13
Italy	9	1	8	10
Belgium	8	1	7	11
Greece	4	1	4	9
Germany	7	1	7	9
Slovenia	5	1	4	5
Ireland	1	1	1	5
Austria	5	-	5	6
France	5	-	5	5
Poland	4	-	4	6
Finland	4	-	4	6
Portugal	4	-	4	4
Lithuania	2	-	2	3
Norway	2	-	2	2
Czech Republic	2	-	2	2
Estonia	2	-	2	2
Switzerland	2	-	2	2
Mali	1	-	1	2

*One participation/institution by: Croatia, Cyprus, Turkey, Malta, Iceland, Hungary, Romania, Bulgaria, Ukraine, Slovakia, Russia, Israel, Canada, Argentina, Botswana, South Africa, Sudan, Uganda, Philippines, Vietnam, Bangladesh; †Seventh Framework Programme; ‡Sixth Framework Programme; §Fifth Framework Programme; ‖Life sciences and technologies for developing countries; ¶Specific program of research and technological development; **Many countries were simultaneously both the project leader and the participant (through another institution from the same country) within the same project. Thus, the total number of projects for a given country does not equal the sum of its leaderships and participations.

Table 2 General data about programs included in the study

Project name	Program	Number of institutions	
		By project	By country
Polypharmacy in chronic diseases: Reduction of Inappropriate Medication and Adverse drug events in elderly populations by electronic Decision Support	FP7	6	1.2
Quality and costs of primary care in Europe	FP7	6	1.2
New and more individualised population-based screening for cardiovascular disease; from a RCT including self-assessments, primary care and coronary artery calcification score to modelling risk-benefit	FP7	2	2
REsearch into POlicy to enhance Physical Activity	FP7	10	1.25
Self-care Support for People with Long Term Conditions, Diabetes and Heart Disease: A Whole System Approach	FP7	7	1.17
Learning from international networks about errors and understanding safety in primary care	FP7	12	1.5
Assessing the over-the-counter medications in primary care and translating the theory of planned behaviour into interventions	FP7	11	1.38
Human Resources for Primary Health Care in Africa	FP7	9	1.13
Improving the Continuity of patient care Through Identification and implementation of Novel patient handoff processes in Europe	FP7	9	1.5
Optimizing delivery of health care interventions	FP7	19	1.9
The appropriateness of prescribing antibiotics in primary health care in Europe with respect to antibiotic resistance	FP7	14	1.56
Changing behaviour of health care professionals and the general public towards a more prudent use of anti-microbial agents	FP6	12	1.71
Health alliance for prudent prescribing, yield and use of antimicrobial drugs in the treatment of respiratory tract infections	FP6	15	1.67
Implementation of patient involvement instruments to improve general practice care for older people in Europe	FP5	14	1.27
Prediction of future episodes of depression in primary medical care: development of a risk factor profile	FP5	5	1
The aged in home care project	FP5	9	1
The care and management of services for older people in europe network	FP5	38	3.8
Primary health-care in later life: improving service in Bangladesh and Vietnam	FP5	4	1
Learning organised through teams	LEONARDO DA VINCI	5	1
Comparative study on task profiles of general practitioners in Europe	PECO/ COPE-RNICUS	5	1
Collaborative project on community drug use: enhancing the impact of essential drugs programmes	STD 3	5	1.25
Logic Engineering in General Practice, Oncology and Shared Care	AIM 2	8	1.33

21 countries (including Croatia, the new EU member state), both from the EU area and beyond, that have successfully applied for and participated in a project together through a single institution.

Discussion

Our results showed that the Netherlands was the country with the largest number of leaderships and partnerships in the EU funded

projects in the field of family medicine. This could be the result of a long-lasting tradition of cooperation networks between the family medicine research work in Netherlands and other EU countries. The Netherlands School of Primary Care Research (CaRe) is a center of research in primary care and also a virtual institute which promotes medical doctor and doctoral (MD/PhD) programs for primary care (family medicine, health science, epidemiology, ethics, medical informatics, nursing). Founded in 1995, it is recognized by the Royal Netherlands Academy of Sciences as a research center of excellence. The research program focuses on promotion and health education, determinants of long-term outcome of illness, effectiveness of diagnostic and therapeutic interventions, quality of care, and international aspects of primary care. Three practice-based research networks are linked to the research program (5). By cooperating with almost all European and some Asian countries, the family medicine programs of Netherlands have demonstrated great openness, cooperativeness, and readiness for a high level of international cooperation.

So far, Croatia was a partner in a single FP7 Health project related to the field of family medicine. In 2013, Croatia became a full member of the European Union which will, we hope, contribute to its better and higher quality cooperation in the field of all European research projects. Improving the overall level of cooperation is very important. Learning from the Dutch example would be a fine start. The existing four research centres (one department of family medicine at each of the four medical schools in Croatia), should establish close cooperation and coordination of research work. They should also engage in joint applications for programs (in partnership with the most successful institutions from different countries in this field) in order to establish continuity.

Limitations of the study

It would have been useful to additionally analyse the number of family medicine practitioners in the listed countries to determine its possible correlation with the number of projects but, sadly, there is not enough data available for this. This study was limited by the poor data availability concerning all of the project participants for earlier project cycles. Many otherwise eligible projects (466) listed only the country of the project leader and nothing else and thus had to be excluded, bringing the count down to 225. Also, it is possible that there is a time lag between studies beginning and their entry into the database, so studies which began at the very end of 2012 would not have appeared by February 2013, when the final search was conducted.

Conclusion

Albeit our study is a modest snapshot analysis, the approach we employed revealed interesting results, which can serve as an indicator of the state of family medicine research funding in a given country. It may be useful to widen this approach by analysis of the level of correlation of number and size of grants won by different countries with their respective scientific production, schemes of training, relative number and organization of physicians, workload and a number of other factors that potentially affect scientific excellence in family medicine (and other parts of medicine). This is of utmost importance for the countries which appeared unsuccessful in this analysis because the success in winning European Union research grants and participating in them may indeed indicate the necessity to review the state of art in this important health profession in the country in question.

Acknowledgements: Heartfelt thanks to Professor Matko Marušić for the idea, encouragement, and great help during writing.

Authors' contributions: Conception and design: IP and LB; Acquisition, analysis and interpretation of data: IP; Drafting the article: IP and LB, Revising it critically for important intellectual content: LB and IP.

Conflict of interest: The authors declare that they have no conflict of interest.

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Short communication

Acta Medica Academica 2014;43(1):87-91
DOI: 10.5644/ama2006-124.105

"Fundamental communication skills in medical practice" as minor elective subject

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Received: 24 June 2013
Accepted: 20 March 2014

Objective. Poor and inadequate communication affects the therapeutic relationship between doctors and patients. Guided by this idea, we organized a minor elective course entitled "communication skills". We wanted to bring closer to the students the holistic approach of the family physician to the patient, the importance of the family, its impact on the patient and vice versa, and the significance of the local community and its influence on an individual's health. The aim of this article is to explain how we organized this elective course. **Methods.** The course was organized in the form of 12 hours of theory (3 lectures and 9 seminars) and 24 hours of practical training. There were 26 students from all years. Through theory, and even more through the practical part the students met with different types of patients. **Results**. At the end of the course, students in lower years were evaluated by means of an interview, and graduate students through a practical test – a conversation with a patient. The initial results, including the students' grading of this course, were highly encouraging. Both teachers and students were highly satisfied on completion of the course. **Conclusion.** Content on communication training is rare in teaching. Practicing communication skills will empower the doctor - patient therapeutic relationship.

Key words: Family practice, Health communication, Physician-patient relations, Medical students.

Introduction

Communication is simply the act of transferring information from one place to another, whether this be vocally (using voice), in writing (using printed or digital media such as books, magazines, websites and emails), visually (using logos, maps, charts and graphs) or non-verbally (using body language and/or gestures). How well this information may be transmitted and received is a measure of how good our communication skills are (1). Knowledge of, and skills in, communication are necessary for many professions, especially those in the areas of health, education, and economics (2). An integral part of a doctor's job is communication and interaction with the patients (3-4), including forming a cohesive relationship with patients, as well as effective diagnosis, treatment and therapy, which constitute the keys to successful and effective medical practice (4). When done well, such communication produces a therapeutic effect for the patient, as has been validated in controlled studies. However, the communication skills of the busy physician often remain poorly

developed, and the need for established physicians to become better communicators continues (3). When doctors use communication skills effectively, both they and their patients benefit. Firstly, doctors identify their patients' problems more accurately. Secondly, their patients are more satisfied with their care and can better understand their problems, examinations and tests, and treatment options. Thirdly, patients are more likely to adhere to treatment and to follow advice on behavior change. Fourthly, patients' distress and their vulnerability to anxiety and depression are lessened. Finally, the doctors' own wellbeing is improved (5).

A letter by the wife of a patient describes the importance of communication: "Is there any place in the world where people feel more miserable than in the basement of a hospital, sitting for hours in the hallway, waiting, and no one even asks if he needs it where it did not matter .... and on the door says: Do not knock, do not disturb! Wait! Get out! Is there a place worse than this, where you are just statistical data, a case number, and not a name and surname? The "gods" pass by in white, small and large, with deadly serious faces, stethoscopes in their pockets or around the necks, while young women and the tall young men with no eyelashes and eyebrows, with sad eyes and a look of fear, are waiting and waiting. I am with them. Nothing should be like this: just one smile is enough, just a look of understanding, something like 'do not be afraid! ..." (2).

The manner in which a physician communicates information to a patient is as important as the information being communicated. Patients who understand their doctors are more likely to acknowledge health problems, understand their treatment options, modify their behavior accordingly, and follow their medication schedules. In fact, research has shown that effective patient-physician communication can improve a patient's health as quantifiably as many drugs - perhaps providing a partial explanation for the powerful placebo effect seen in clinical trials (3). Listening is an important skill for family physicians. It can help improve the diagnosis of patients' problems, it can help with an understanding of psychosocial issues, and it may even help to avoid a lawsuit (6-7). However, listening is learned behavior. It is not a passive activity but one that requires skill and practice (7).

Communication in family practice

Traditionally, communication was incorporated in medical school curricula informally as part of rounds and faculty feedback, but without any specific or intense focus on skills of communicating per se. The reliability and consistency of this teaching method left gaps, which are currently getting increased attention from medical schools and accreditation organizations (8). Formal training programs have been created to enhance and measure specific communication skills. Many of these efforts, however, focus on medical schools and early postgraduate years and, therefore, remain isolated in academic settings. Thus, the communication skills of the busy physician often remain poorly developed, and the need for established physicians to become better communicators continues (3). Increasing experience does not automatically improve communication skills but some deliberate practice seems to be necessary and must be sought and developed (9).

The aim of this study was to develop an undergraduate medical course which exposes students to the holistic approach by a family physician to the patients, the importance of the family, its impact on the patient and vice versa, and the significance of the local community and its influence on an individual's health.

Methods

The curriculum of the subject 'Family Practice' included lectures and seminars on communication from the time when the Department was founded. Emphasizing the importance of communication, there was a need to organize an elective course on this topic. According to the Curriculum with syllabus for the academic year 2011/2012 of the Medical Faculty (10), our Department designed the elective subject entitled "Fundamental communication skills in medical practice". There were 26 students of all ages (from freshmen to graduates)_out of 326 students (8%) who enrolled in the subject. Most students were from the freshman (first) year level.

The course was organized in the form of 12 hours of theory and 24 hours of practical training. Theoretical classes were organized in the form of lectures and seminars, including:

- Communication skills in medicine - general terms;
- Types of communication;
- Techniques of good communication;
- Effective medical interview;
- Difficult patients;
- Communication with special patient groups (child, adolescent, third age);
- Communication in special medical situations (emergency, palliative care);
- Communication in a team with colleagues and the media.

The Chair of Family Medicine created a plan and program for the Course according to the Curriculum of the Faculty. Four teachers, specialists in Family Medicine, were included in the teaching. At the end of Course we organized an examination for students, but they also evaluated the subject. Students completed a questionnaire measuring their satisfaction with the teaching. The questionnaire was standardized by the University and it is identical for all subjects at the University.

Results

The practical teaching process was organized in the clinic in which the teacher worked. The kind of communication (verbal and nonverbal) were discussed and practiced, in the family practice surgeries. Types of communication skills were practiced through role playing, representing the different situations in which Family physicians find themselves: for example: a patient who requires something, a patient with multiple problems, a patient who denies everything you tell him, an upset patient, etc. Students met with several types of difficult patients, and experienced the role of the family doctor as gatekeeper of the health system, and different forms of communication with other health workers. Senior students solved some of the health problems of patients independently under the supervision of teachers. Younger students (students of lower years) were observers and they did not practice directly with the patients, but were included in discussions on each patient within the group.

Evaluation was done by a similar principle. Teachers evaluated the lower year students through an interview, and graduate students (fourth - sixth year of study) who already possess certain clinical skills, were tested practically in contact with a patient. The subject was evaluated very highly. None of the students assessed the elective subject as 'poor', 'fair' or 'good'. The practical part of the subject, as well as the organization of subjects were assessed as excellent. All other elements of the subject were ranked as 'excellent' by at least 80% of respondents (Table 1).

Table 1 Students' evaluation of the minor elective subject "Communication skills"

Evaluation of subject	Students' evaluation (n=26)	
	Very good	Excellent
	n (%)	n (%)
Evaluation of subject in general	1 (3.8)	25 (96.2)
Grading of the lectures	2 (7.7)	24 (92.3)
Grading of the seminars	3 (11.5)	23 (88.5)
Grading of exercise / practical work	-	26 (100)
Grading of teaching organization	-	26 (100)
Grading of the examination	5 (19.2)	21 (80.8)

Discussion

With this article we have tried to share our experiences of learning communication skills through an elective course. In the published literature and other experiences, which show significant improvements in communication with patients after training (11-12), but also within the team (13-14). Brock et al. (11) describe the results before and after The Team Strategies and Tools to Enhance Performance and Patient Safety (Team STEPPS) communication training model.

Significant successes have been recorded in team communication, motivation, training and utility of self-efficiency (11). Students in Iran highlight the possible consequences of deficiencies in poor communication and the importance of learning communication skills during their studies and their incorporation into the medical school curriculum (15). Our students had a similar attitude compared to students around the world regarding the importance of good communication skills. The student's comments and ratings of items supported the new communication skills subject and have motivated us to further improve teaching of the elective course on communication skills.

We expect that an increase in communication exercises will give better results in the physician - patient relationship, and thus contribute towards a healthier population.

Authors' contribution: Conception and design: AZ, ECO; Acquisition, analysis and interpretation of data: AZ; Drafting the article: AZ, ECO; Revising it critically for important intellectual content: AZ, ECO.

Conflict of interest: The authors declare that they have no conflict of interest.

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Acta Medica Academica 2014;43(1):92-96
DOI: 10.5644/ama2006-124.106

Delayed diagnosis of cleidocranial dysplasia in an adult: A case report

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Received: 25 June 2013
Accepted: 27 December 2013

Objective. To describe a rare case of cleidocranial dysplasia, an autosomal dominant inherited disease involving the skeleton and teeth, with delayed diagnosis. **Case report**. We report a 24-year-old man with cleidocranial dysplasia admitted with hearing loss, rhinolalia, dyspnea and fatigue. Partial absence of clavicles, a bell-shaped ribcage, an open frontal fontanel, unerupted permanent teeth and broad sutures were identified at radiographic examination. **Conclusion**. Cleidocranial dysplasia is very rare, and is commonly missed or diagnosed late. Radiographic findings are essential for diagnosis. An open frontal fontanel is a particularly important finding for neurosurgeons in diagnosis. We describe this rare case and discuss the clinical features of CCD.

Key words: Open frontal fontanel, Marie and Sainton's disease, Cleidocranial dysplasia, Autosomal dominant.

Introduction

Cleidocranial dysplasia (CCD) is an autosomal dominant inherited disease (1) caused by mutations in the RUNX2 gene on chromosome 6p21 encoding a transcription factor involved in osteoblast differentiation and skeletal morphogenesis. CCD was first described by Pierre Marie and Paul Sainton in 1898 (2) and is also known as Marie and Sainton's disease, mutational dysostosis or cleidocranial dysostosis (3). Major characteristics of CCD are delayed closure (ossification) of the fontanels, premature closing of the coronal suture, a protruding mandible, mid-face retrusion, abnormal dentition, including delayed eruption of secondary dentition, failure of primary teeth eruption, supernumerary teeth with dental crowding and malocclusion, and clavicular hypoplasia (4). The nasal bridge is broad due to the wide distance between the orbits (hypertelorism), and patients are more likely to have a high-arched or possibly cleft palate, short stature and scoliosis of the spine. Hand abnormalities are brachydac-

tyly, tapering fingers, and short, broad thumbs (4). Frontal bossing also occurs because of delayed closure of the anterior fontanel and metopic sutures. ENT manifestations include recurrent paranasal sinus and middle ear infections resulting in conductive hearing loss. Although CCD is a disease with autosomal dominant inheritance, spontaneous genetic mutations have also been reported. Many cases are caused by *de novo* mutation (4). Diagnosis of CCD is based on clinical and radiological findings.

We describe a case of CCD first diagnosed at the age of 24 years. The patient had mild symptoms and therefore may not have presented to medical professionals previously. It is also a fact that the incidence is so low that the diagnosis is often unrecognised, even when a patient does present.

Case Report

A 24-year-old man was admitted to the neurosurgery clinic for routine health checks before starting military service. He exhibited symptoms of hearing loss in the right ear, rhinolalia, dyspnea and fatigue. He also had a history of recurrent right middle ear infection. Physical examination revealed delayed closure of the frontal fontanel, a protruding mandible, hypertelorism, frontal bossing, a bell shaped rib-cage, deciduous dentition and delayed eruption of permanent teeth, and partial absence of clavicles. The most interesting findings at physical examination were the open frontal fontanel, extensive mobility of the shoulders due to partial absence of clavicles and his bell shaped chest, as observed at chest radiography (Figure 1).

Cranial radiography and cranial CT scans revealed multiple teeth in both the jaw and maxillary sinuses (Figure 2a, and Figure 2b), open skull sutures, delayed closure of the frontal fontanel, multiple wormian bones, especially in the lambdoid sutures (Figure 2c and Figura 2d), and narrowing of the internal acoustic canal due to thickness of the petrous bone. Otolaryngological examination revealed a submucosal cleft palate and central perforation in the right

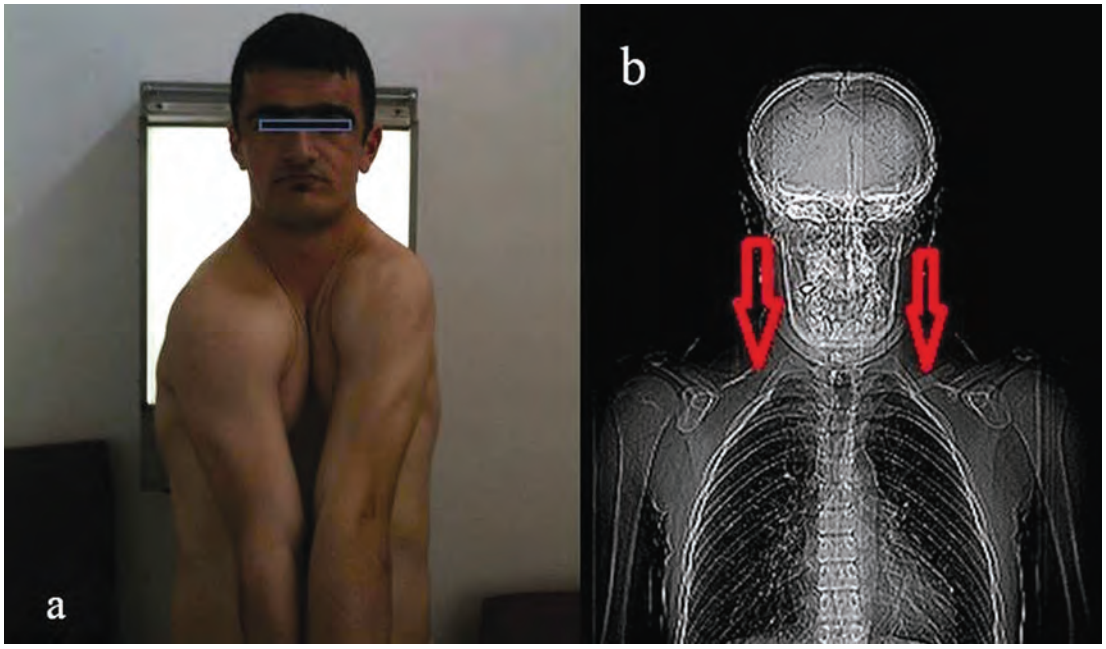

Figure 1 Extensive mobility of shoulders (a) and partial absence of clavicles (red arrows) and bell shaped rib-cage on the chest radiography (b).

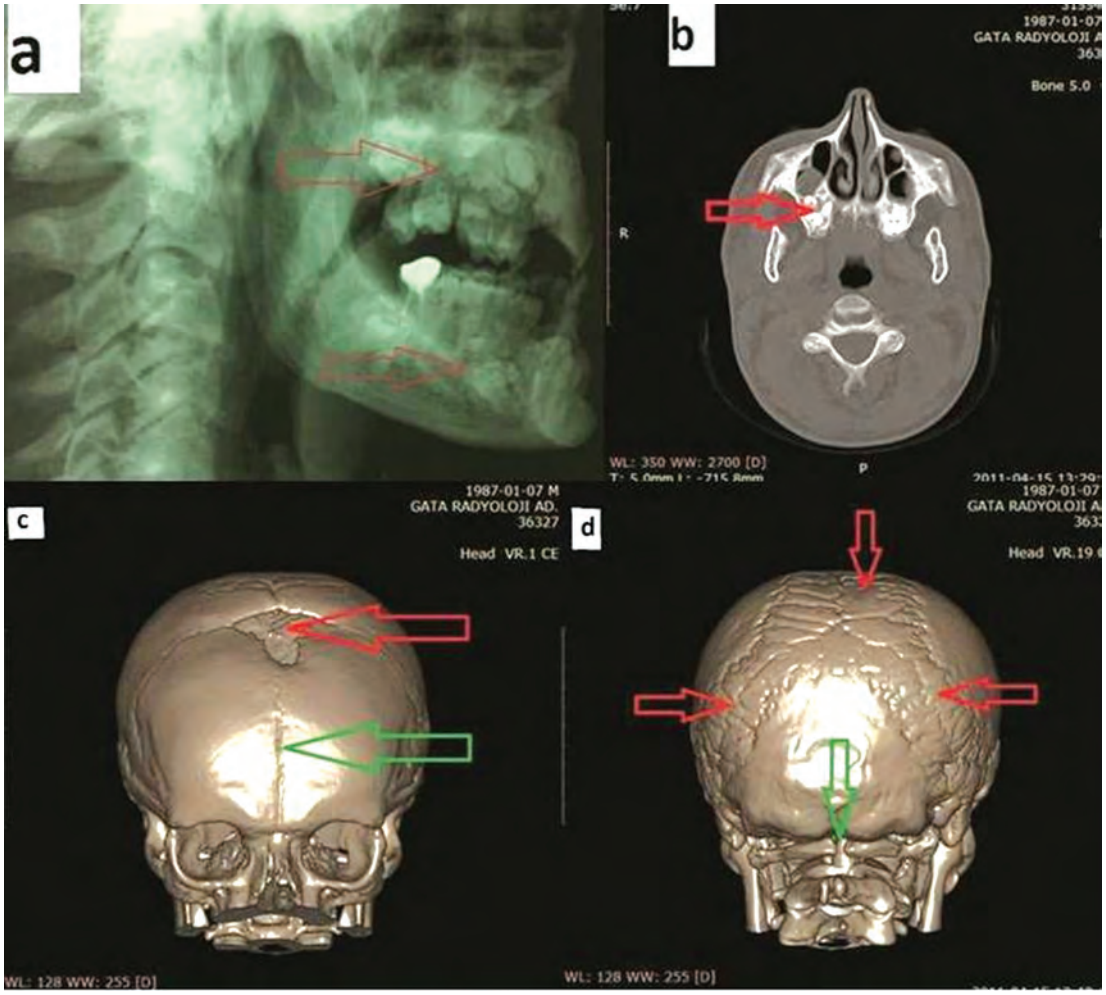

Figure 2 Plain radiographic demonstration of delayed permanent teeth in both jaws (a), and CT scan showing unerupted permanent teeth in the maxilla (b). CT scan showing the delayed closure of the frontal fontanel (red arrow) and frontal groove, resulting from incomplete ossification of metopic suture (green arrow) (c). CT Scan showing the broad sagittal and lambdoid sutures and wormian bones close to lambdoid sutures (red arrows), and open posterior arcus of the axis because of delayed ossification (green arrow) (d).

tympanic membrane. A 40-dB conductive hearing loss in the right ear was detected at pure-tone audiometry. The patient was diagnosed for the first time with CCD, based on physical examination of the head and oral cavity and X-ray and CT imaging findings.

Discussion

CCD is a skeletal dysplasia characterized by delayed fontanel closure, hypoplastic or aplastic clavicles and various dental abnormalities (4). Frontal bossing, delayed closure of the frontal fontanel and excessive mobility of the shoulder girdle are the most common and significant findings in CCD (1, 3). Partial or complete absence of clavicles permits the shoulders to be brought forward into close proximity to the chest. Hypertelorism is another common finding associated with frontal bossing (5). This develops as the result of delayed closure of the metopic suture and frontal fontanel (1). The most important and reliable diagnostic method is radiographic evaluation. Radiographic findings of CCD are characteristic and include

broad cranial sutures, an open frontal fontanel persisting until adulthood, partial or complete absence of the clavicles, numerous wormian bones and large numbers of unerupted supernumerary teeth, bell shaped chest, etc (1, 3).

Patients with CCD should be monitored for evidence of conductive or sensorineural hearing loss, which may be due to structural abnormalities of the ossicles, sclerosis of temporal bone together with middle ear problems due to abnormal formation of palate and Eustachian dysfunction, and cochlear or eighth nerve problems (6). Our patient had a submucosal cleft palate, causing rhinolalia, and Eustachian dysfunction resulting in recurrent middle ear infections. The 40-dB conductive hearing loss was due to tympanic membrane perforation, a sequela of recurrent middle ear infections and probably attributable to structural abnormalities of the ossicles or temporal bone sclerosis.

Our patient had also suffered from fatigue and dyspnea. His bell shaped chest was observed on his chest radiography. Decreased respiratory capacity due to abnormal chest shape is the probable cause of fatigue and shortness of breath.

The management strategy for CCD relies on treatment of the manifestations of the syndrome. Dental manifestations can be treated by removal of the supernumerary teeth followed by surgical repositioning of permanent teeth (4). Prosthetic replacements can be used to improve esthetic appearance. Timely treatment of recurrent middle ear infections, and consideration of the possibility of tympanostomy tubes, is necessary to prevent chronic sequelae such as tympanic perforation, adhesive otitis media or conductive hearing loss, as reported in our case. Craniofacial surgery may be required for the correction of skull anomalies (7). Coxa vara is treated with corrective femoral osteotomy. Clavicular fragments can be removed in order to decompress the brachial plexus in cases of symptomatic nerve compression, accompanied by pain and numbness (8). In the case of an open fontanel, appropriate headgear may be recommended for protection against injury. Pregnant women with CCD should be monitored closely for cephalopelvic disproportion. Caesarean section may be the preferred method of delivery in such cases.

CCD can be a challenging syndrome to diagnose and manage, exhibiting multiple developmental deformities of the skeletal system. Early diagnosis is crucial for the timely commencement of appropriate treatment. Successful treatment of patients with CCD requires an interdisciplinary approach and collaboration among specialists, the patient and the family. Even though most cases are diagnosed during childhood or adolescence, diagnosis may be delayed until adulthood if the symptoms and signs are not severe. In our opinion, this report will contribute to the literature and promote awareness of the importance of early diagnosis of this very rare syndrome.

Conclusion

CCD is a rarely occurring syndrome of skeletal abnormalities, characterized by hypermobility of the shoulders, open fontanels and numerous skeletal findings. Clinical findings are commonly present at birth, but unfortunately diagnosis is not usually made at this early stage. The most specific neurosurgical finding is an open fontanel, and the clinician should be aware of this finding in order to diagnose CCD.

Authors' contributions: Conception and design: CG and EA; Acquisition, analysis and interpretation of data: CG, EA and SP; Revising it critically for important intellectual content: EAA, EA, CG and SA.

Conflict of interest: The authors declare that they have no conflict of interest.

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Acta Medica Academica 2014;43(1):97-98
DOI: 10.5644/ama2006-124.107

Vein of trolard sign on noncontrast computed tomography in Behcet's disease

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A 45-year old male with Behcet's disease (BD) with prior oral aphthous and genital ulcers diagnosed outside our facility presented to the emergency department (ED) with two weeks of progressive headaches with abrupt onset dysarthria, left lower facial and left arm weakness. The patient had recently moved from another state to our region and stopped taking his warfarin for history of deep vein thrombosis, and had not established care with a rheumatologist, neurologist or primary care physician. Because of his unknown history at the local emergency room a noncontrast computed tomography (CT) head was originally interpreted as negative for acute stroke (Figure 1A). His symptoms did transiently improve in the ED and he was later discharged home. Subsequently he returned after a generalized tonic-clonic seizure, and a second noncontrast CT (Figure 1B) showed a hyperdense right cortical vein of Trolard (VOT) and delta (Δ) signs indicating saggital sinus thrombosis and a right hemisphere subcortical hemorrhage. He was transferred to our facility for a possible aneurysmal subarachnoid hemorrhage. At our facility we performed a CT venogram which confirmed the localization of the venous thrombus (Figure 1C and 1D). The patient was placed on IV heparin initially, and on warfarin and clinically improved back to normal within a few days. He was discharged from our hospital with followup at our clinic with a rheumatology expert and neurology clinic. Cerebral venous thrombosis (CVT) is an important complication in BD (1, 2) which may result in significant morbidity or mortality. In this patient, with history of BD with headache, a high degree of clinical suspicion should be raised for CVT. Therefore, the initial noncontrast CT head should be examined closely for abnormalities, and in this case was found to be consistent with CVT. We propose the "VOT sign" as a new, highly specific finding on noncontrast head CT suggestive of CVT which should prompt consideration of a CT venogram to confirm the diagnosis. The "VOT sign" is an useful sign even in patients with unknown history because it is highly abnormal and to our knowledge it has not been described before. Noncontrast CT head may be falsely negative in 10-20% of cases with proven CVT (3) compared to CT or MR venography. Mimics of a positive hyperdense sagittal sinus include causes of elevated hematocrit such as polycythemia, dehydration, or CVT. Management of CVT is initial anticoagulation with IV heparin followed by vitamin K antagonists such as warfarin. Intracranial hemorrhage that occurs as a consequence of CVT is not a contraindication for anticoagulation (3), although this remains controversial.

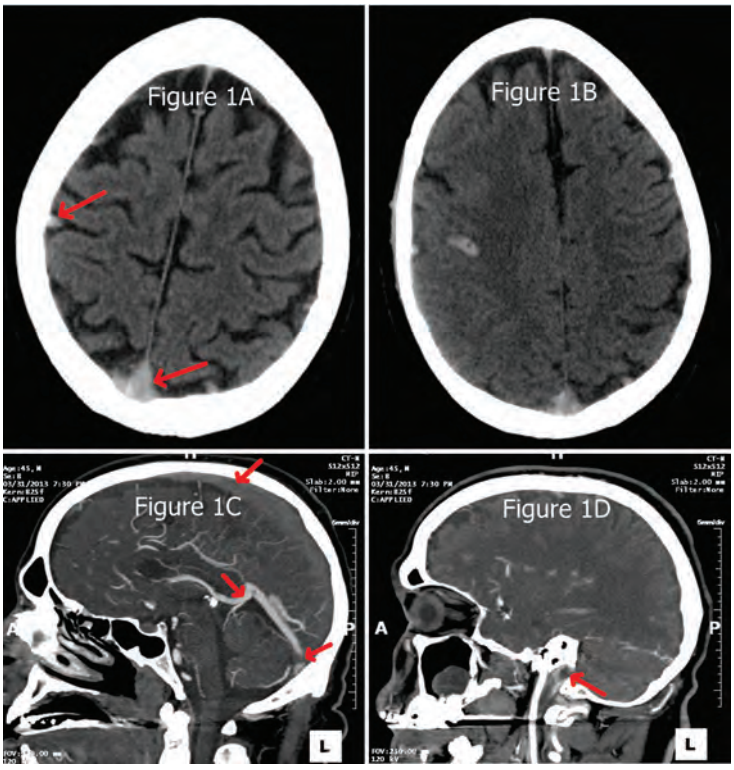

Figure 1A – Non contrast CT - Vein of Trolard (VOT) (left arrow) & Delta (Δ) Signs (bottom middle arrow); Figure 1B – Non Contrast CT - VOT and Δ signs, as well as right subcortical parenchymal hemorrhage from venous hypertension; Figure 1C – Sagittal CT venogram – Sagittal sinus thrombosis (top arrow), patent vein of Galen (middle arrow) and thrombus at the confluence of the transverse and straight Sinuses (bottom right arrow); Figure 1D – Sagittal CT venogram – Thrombus at the top of the jugular vein at the jugular foramen (arrow).

Authors' contributions: Conception and design: WDF, TR; Acquisition, analysis, and interpretation of data: WDF, TR; Drafting the article: WDF, TR; Revising it critically for important intellectual content: WDF, TR.

Conflict of interest: The authors declare that they have no conflict of interest.

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Received: 28 June 2013; Accepted: 22 January 2014

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Acta Medica Academica 2014;43(1):99-101
DOI: 10.5644/ama2006-124.108

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*Data for this survey were collected from PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) using the keywords Bosnia and Herzegovina and 2013.

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by Nerma Tanović

Acta Medica Academica 2014;43(1):102
DOI: 10.5644/ama2006-124.109

Dušan Kecmanović, member of the Academy of Sciences and Arts of Bosnia and Herzegovina **(1942-2014)**

Slobodan Loga

Dušan Kecmanović died suddenly on 6th April 2014 in Sydney Australia. He was a member of the Academy of Sciences and Arts of Bosnia and Herzegovina, and was previously a professor at the Medical Faculty in Sarajevo and one of the best known psychiatrists in the world from this region. Dušan Kecmanović was born in Belgrade in 1942 and from 1945 he lived in Sarajevo until the beginning of the war (1992-1995) when he emigrated to Australia. He completed his education and training in Sarajevo. After four years of elementary school, he attended classical high school. While he was still in high school, he spent much of his time reading books. As well as fiction, he was interested in books on psychology, sociology and philosophy. Even then he had a full knowledge of French. His knowledge of German enabled him to read the collected works of Arthur Schopenhauer in the Gothic script. He learned English after French and German. He finished high school as the best student in his year, went on to study at the Medical Faculty in Sarajevo and graduated within five years with an average grade of 9.4. He was then employed at the Psychiatric Clinic in Sarajevo, where he specialized in psychiatry. He ended his post-graduate studies in "The bases of scientific research" by writing his master's thesis entitled "Patients discharged against the advice of the doctor from the closed psychiatric ward." He attained his PhD from Belgrade University in 1975, on the thesis "An attempt at thematic and methodological conceptualization of social-psychiatric activities". The first book he wrote as a specialist student was a collection of essays under the joint title "Between the normal and the pathological", which aroused significant attention amongst psychiatrists. Very soon after completing his specialized studies he turned his attention to social psychiatry. In 1975 he published the book "Social Psychiatry with the Psychiatric Sociology", which very soon became a key textbook at university centres throughout Yugoslavia. Later the focus of his professional interest shifted to topics related to the social role of psychiatry and the mentally disturbed, as well as ethical issues in psychiatry. In 1990 he was elected to be a corresponding member of the Academy of Sciences and Arts of Bosnia and Herzegovina. When the war broke out, he was a full professor at the Medical Faculty and a full professor of political psychology at the Faculty of Political Sciences in Sarajevo. During the war he emigrated to Australia and was the first psychiatrist to have his psychiatry degree recognized without taking any exams, and he was declared a member of the Royal Australian and New Zealand College of Psychiatrists. The death of Dušan Kecmanović is a major and irreplacable loss for psychiatry in Bosnia and Herzegovina. His influence on the progress of psychiatry in Bosnia and Herzegovina, and beyond, was enormous. Moreover, he represented Bosnian psychiatry throughout the world through his significant reputation. A well-rounded, educated man, who spoke three world languages, he reached the highest levels in the theory and practice of the science of psychiatry. He grew up in a family where spiritual values were paramount and the written word was nurtured. Thanks to this, and his tireless work, Dušan Kecmanović has left a legacy of numerous books, articles in journals and useful ideas for future study. He will be remembered as an excellent speaker and superb polemicist, who always had good arguments and knowledge on his side.

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sional, or thoroughly checked by a native speaker with experience in writing scientific and medical manuscripts in English. Revision of the language is the responsibility of the author. All manuscripts should be spellchecked using a Microsoft Word or Dorland's spellchecker before they are submitted. Spelling should be US English or British English, but not a mixture. On the grounds of poor English manuscripts may be sent back to an author for rewriting or language correction.

Font and spacing. The manuscript should be prepared in Microsoft Word format (for PC, 6.0 or a later version). Paper version should be typewritten on white bond paper of A4 size, with margins 3 cm each. Write on one side of each sheet, using a font not smaller than 12 points, preferably Times New Roman or Arial. All pages must be numbered. Prepare texts with double spacing (except those of tables, which are made with table tools in Word or in Excel). Double spacing of all portions of the manuscript (including the title page, abstract, text, acknowledgments, references, and legends), makes it possible for editors and reviewers to edit the text line by line, and add comments and queries, directly on the paper copy.

Length. The length of a manuscript depends on its type. On the title page, author should specify total word count and/or character count. Microsoft Word can count them for you. With **double spacing** (2000 characters with spaces per page), the limits are as follows:

- **Editorial** – up to 3 pages (maximum count 6000 characters with spaces) and maximum 15 references.
- **Review article** – from 12 to 20 pages (maximum count 30000 characters with spaces) and maximum 40 references.
- **Original research study** – from 12 to 15 pages (maximum count 30000 characters with spaces).
- **Original (scientific and professional) article** – from 12 to 15 pages (maximum count 30000 characters with spaces).
- **Short communication** – up to 5 pages (maximum count 10000 characters with spaces), only two graphical display (figure or table) and up to 5 references and up to 3 authors.
- **Statistical and methodological compilations** – up to 16 pages (maximum count 32000 characters with spaces).
- **Case reports and letters** – up to 3 pages (maximum count 10000 characters with spaces), a maximum of 2 figures or tables and no more than 15 references.
- **Images in clinical medicine** – is an article providing one or two fascinating pictures in black and white or in color. It can be clinical or technical on a patient or part of a patient, for instance an x-ray or MRI image or a histological document. The picture is accompanied by a short text (a maximum of 300 words), up to 3 authors, and if necessary 1 to 3 references can be included.
- **Letter to the editor** – up to 3 pages (maximum count 2000 characters with spaces), and up to 5 references.

Organization of the text. The text of original articles is usually divided into sections with the following headings: Introduction, Materials (Patients) and methods, Results, Discussion and Conclusion. This structure is not simply an arbitrary publication format, but rather a direct reflection of the process of scientific discovery. Long articles may need subheadings within some sections (especially the Results and Discussion sections) to clarify their content. Other types of articles, such as case reports, reviews, and editorials, are likely to need other more flexible structure of the text. If possible, use standard abbreviations. Non-standard abbreviations should be defined when first used in the text.

Title page (the first page)

The title page should carry the following information:

1. Type of the article.
2. Title of the article, which should be as short and concise as possible. Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific.
3. A short title (up to 50 characters with spaces), which will appear in the heading of an article in the journal.
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6. Corresponding authors. The name, mailing address, telephone and fax numbers, and e-mail address of the author responsible for correspondence about the manuscript. The name and address of the author to whom requests for reprints should be addressed (if different from the corresponding author), or a statement that reprints will not be available from the authors.

7. Specify sources of support in the form of grants, equipment, drugs, or others, if any and a statement about existence or non-existence of the conflict of interests.

8. Total number of pages, words and characters with spaces (Microsoft Word enables the simple acquisition of these data), number of figures and tables. A word count for the text only (excluding abstract, acknowledgments, figure legends, and references) allows editors and reviewers to assess whether the information contained in the paper warrants the amount of space devoted to it, and whether the submitted manuscript fits within the journal's word limits. A separate word count for the Abstract is also useful for the same reason.

Second page

Abstract and Key words are written on the second page. Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to be careful that abstracts reflect the content of the article accurately. An abstract (250 words) is written without authors' names and institutional affiliations. Its structure should be similar to that of the text. For original articles, the abstract needs to have the structure with the following subtitles: Objective, Materials and methods, Results and Conclusion. Abstracts for Case reports also need to have the following subtitles: Objective, Case report, and Conclusion and for Review articles: Objective, Background, Methods, Discussion and Conclusion. Abstracts for Short communication (150 words) should not be structured but should end with Conclusion. Following the abstract, authors provide, and identify as such, 3 to 5 key words or short phrases that capture the main topics of the article. The key words should not repeat the title of the manuscript. Terms from the Medical Subject Headings (MeSH) list of Index Medicus should be used; MeSH terms are available from: www.nlm.nih.gov/mesh/.

Third page

Should carry the manuscript of article. Text should be under the following headings:

Introduction. Needs to be short and to specify to the reader, clearly and with arguments, reasons for the research presentation, and the novelties that the article brings. In Introduction maximum 3 to 4 pertinent and directly related works need to be cited. At the end of Introduction, an author needs to clearly specify the set aim of the research.

Methods. This part needs to provide the following information: selection and description of participants, precise technical information about all methods (describe the methods, apparatus, and procedures in sufficient detail to allow other workers to reproduce the results; give references to established methods, including statistical methods; identify precisely all drugs and chemicals used, including generic names, doses, and routes of administration and other specificities related to the presented research). Upon reporting about humane experiments, an author needs to indicate if the used procedures were in accordance with the Declaration of Helsinki from 1975 and its amendments from 1983. In addition, there needs to be stated if and which ethical committee gave consent for carrying out the research. A separate subtitle is Statistical Analysis. Authors need to indicate all statistical tests that were used. In addition, there needs to be stated the level of significance selected beforehand (p), that is which value p the authors considered to be statistically important (ex. 0.05 or 0.01, or some other). The results should be stated with pertaining confidence intervals (CI).

The editorship recommends to the authors to follow STARD instructions published in 2003 in the researches of diagnostic accuracy. At the end of the paragraph authors need to state which computer statistical program they have been using, as well as indicate the manufacturer and version of the program.

Results. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. The text must contain a clear designation as to where the tables and illustrations are to be placed relative to the text. Do not duplicate data by presenting it in both a table and a figure.

Discussion. Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. For experimental studies it is useful to begin the discussion by summarizing briefly the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.

Conclusion. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, authors should avoid making statements on economic benefits and costs unless their manuscript includes the appropriate economic data and analyses. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such.

Acknowledge. Anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. List the source(s) of funding for the study and for the manuscript preparation in the acknowledgements section.

Authors' contributions (eg.): Conception and design: MK and OG; Acquisition, analysis and interpretation of data: MK and GL; Drafting the article MK; Revising it critically for important intellectual content: GL and OG).

Conflict of interest (eg.): The authors declare that they have no conflict of interest.

References. Need to be on a separate page. Small numbers of references to key original papers will often serve as well as more exhaustive lists. Avoid using abstracts as references. References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. If the paper has been published in electronic form on PubMed the confirmation of acceptance is not needed. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source. Avoid citing a "personal communication" unless it provides essential information. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication.

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses at the end of a sentence. Use the same number in the reference list. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure.

The titles of journals should be abbreviated according to the style used in Index Medicus. Consult the list of Journals Indexed for MEDLINE, published annually as a separate publication by the National Library of Medicine (available from: www.nlm.nih.gov/tsd/serials/lij.html). Examples of references please see on the following pages.

Tables. Need to be submitted separate from the main text. The preferred software for tables is Microsoft Excel (save each table in a file with single worksheet). Only tables made with table tools in Microsoft Word are acceptable. For the paper version, type or print each table on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text. Use Arabic numerals. Each table needs to have an explanatory title. Place the title above the table. Give each column a short or abbreviated heading. Also, visibly indicate the position of each table in the text, using its assigned numeral at the end of the sentence which is relevant to the table(s). Tables should be positioned in the text where the au-

thor feels is appropriate but the Editor reserves the right to reorganize the layout to suit the printing process. Authors need to place explanatory matter in footnotes, not in the heading. Explain in footnotes of the table all nonstandard abbreviations. For footnotes use the following symbols, in sequence: *, †, ‡, §, ||, ¶, **, ††, ‡‡. Identify statistical measures of variations, such as standard deviation and standard error of the arithmetic mean. *Be sure that each table is cited in the text.* If you use data from another published or unpublished source, obtain permission and acknowledge them fully.

Figures. (illustrations: diagram, photograph, photomicrograph, radiograph, drawing, sketch, picture, outline, design, plan, map, chart, etc.). Need to be submitted separate from the main text. They need to be submitted as photographic quality digital prints or, exceptionally, as professionally drawn and photographed original illustrations. Figures should be in a digital format that will produce high quality images. Formats recommended include: JPEG, GIF, TIFF, Microsoft Word, Excel. Sending original photographs and slides is permissible when they cannot be digitized without professional help. In this case, send an explanation in the cover letter. Using Arabic numerals, number figures consecutively in the order of their first citation in the text. Also, visibly indicate the position of each figure in the text, using its assigned numeral in parentheses. Figures should be positioned in the text where the author feels is appropriate but the Editor reserves the right to reorganize the layout to suit the printing process.

Supply a legend for each figure. Titles and detailed explanations belong in the legends, however, not on the figures themselves. Figures should be made as self-explanatory as possible. Letters, numbers, and symbols on figures should therefore be clear and even throughout, and of sufficient size that when reduced for publication each item will still be legible. Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. If photographs of people are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Legends for Figures need to be included in the main manuscript text file, on a separate page immediately following the references. Type or print out legends using double spacing. For each figure, the following information should be provided: figure number (in sequence, using Arabic numerals – i.e. Figure); title of the figure; all necessary explanations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

Units of measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Abbreviation, Acronyms and Symbols

If possible for metric units use standard abbreviations. Non-standard abbreviations should be defined when first used in the text.

Sample references

Articles in journals

Standard journal article (*List the first six authors followed by et al.*):

> Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002;347(4):284-7.

More than six authors:

> Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Organization as author:

> Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension. 2002;40(5):679-86.

No author given:

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

Volume with supplement:

Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. Headache. 2002;42(Suppl 2):S93-9.

Issue with supplement:

Glauser TA. Integrating clinical trial data into clinical practice. Neurology. 2002;58(12 Suppl 7):S6-12.

Issue with no volume:

Banit DM, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. Clin Orthop. 2002;(401):230-8.

Letters or abstracts:

Tor M, Turker H. International approaches to the prescription of long-term oxygen therapy [letter]. Eur Respir J. 2002;20(1):242.;
Lofwall MR, Strain EC, Brooner RK, Kindbom KA, Bigelow GE. Characteristics of older methadone maintenance (MM) patients [abstract]. Drug Alcohol Depend. 2002;66 Suppl 1:S105.

Article republished with corrections:

Mansharamani M, Chilton BS. The reproductive importance of P-type ATPases. Mol Cell Endocrinol. 2002;188(1-2):22-5. Corrected and republished from: Mol Cell Endocrinol. 2001;183(1-2):123-6.

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Malinowski JM, Bolesta S. Rosiglitazone in the treatment of type 2 diabetes mellitus: a critical review. Clin Ther. 2000;22(10):1151-68; discussion 1149-50. Erratum in: Clin Ther. 2001;23(2):309.

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Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sacderived precursor cells. Blood. 2002 Nov 15;100(10):3828-31. Epub 2002 Jul 5.

Books and other monographs

Personal author(s):

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Editor(s), compiler(s) as author:

Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 2nd ed. New York: McGraw-Hill; 2002.

Organization(s) as author:

Royal Adelaide Hospital; University of Adelaide, Department of Clinical Nursing. Compendium of nursing research and practice development, 1999-2000. Adelaide (Australia): Adelaide University; 2001.

Chapter in a book:

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Conference paper:

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Dissertation:

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

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Newspaper article:

Tynan T. Medical improvements lower homicide rate: study sees drop in assault rate. The Washington Post. 2002 Aug 12;Sect. A:2 (col. 4).

Dictionary and similar references:

Dorland's illustrated medical dictionary. 29th ed. Philadelphia: W.B. Saunders; 2000. Filamin; p. 675.

Electronic material

CD-ROM:

Anderson SC, Poulsen KB. Anderson's electronic atlas of hematology [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

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Chason KW, Sallustio S. Hospital preparedness for bioterrorism [videocassette]. Secaucus (NJ): Network for Continuing Medical Education; 2002.

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Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm.

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Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap. edu/books/0309074029/html/.

Homepage/Web site:

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

Part of a homepage/Web site:

American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2 screens]. Available from: http://www.ama-assn.org/ama/pub/category/1736.html.

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Who's Certified [database on the Internet]. Evanston (IL): The American Board of Medical Specialists. c2000 – [cited 2001 Mar 8]. Available from: http://www.abms.org/newsearch.as.

ISSN 1840-1848