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Osteoarticular complications of brucellosis: The diagnostic value and importance of detection matrix metalloproteinases

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Objectives. Matrix metalloproteinases (MMPs) has been implicated in the pathogenesis of infective, cancer and autoimmune diseases. In this study, we investigated the serum level of MMPs and its clinical importance in human brucellosis. **Patients and methods**. This study included 60 brucellosis patients treated at the Clinic for Infectious Diseases, Clinical Centre, University of Sarajevo. Matrix metalloproteinases serum levels were quantified by ELISA. **Results**. The investigation involved three groups: 30 patients with complications, 30 patients without complications of brucellosis and 30 healthy control examinees. The complications of human brucellosis varied but osteoarticular involvement dominated (n=21/30; 70%). Matrix metalloproteinases serum levels in the patients with complications were highest. The serum level of MMP-1 in patients with complications was the highest at 9.45; in patients without complications it was 3.78 and in the control examinees it was lowest at 3.62 (p=0.001). The serum level of MMP-9 in patients with complications was the highest at 105.66; in patients without complications 64.67, and in the control examinees it was lowest at 37.32 (p=0.001). The serum level of MMP-13 in patients with complications was highest at 138.86; in patients without complications at 64.85; and in the control examinees it was the lowest at 29.55 (p=0.001). Pearson's coefficient showed a statistically significant positive correlation between levels of tested matrix metalloproteinases and development complications in human brucellosis (p=0.001). **Conclusion**. This study showed the diagnostic value and importance of detection of matrix metalloproteinases in human brucellosis. MMPs are a useful serum biomarker for assessment of disease activity

Introduction

Brucellosis is an important public health problem throughout the world, particularly in the Mediterranean region, the Arabian Peninsula, the Indian subcontinent, and parts of Central and South America (1, 2). Brucellosis is primarily an animal disease, and in them it passes as an asymptomatic chronic infection. Infections of humans follow the spread of brucellosis in animals. Clinical findings in brucellosis are non-specific, such as fever, sweat, malaise, anorexia, headache and back pain (1, 2). Diagnosis of brucellosis is on the basis of the clinical picture, epidemiological and anamnestic data and laboratory analysis. Early diagnosis of brucellosis, including adequate antibiotic therapy, has crucial importance for patients, especially for protection from development of complications.

Complications of human brucellosis were registered in 10%-16% patients and osteoarticular involvement dominated (2, 3). The three most common forms of osteoarticular involvement are sacroilitis, spondylodiscitis and peripheral arthritis (3). Loss of bone is a serious complication of localized bacterial infection of the bones or the adjacent tissue. Despite the fact that clinical and imaging aspects of osteoarticular brucellosis have been described widely, the mechanisms involved in this process have not been completely explained (3). The skeleton is a dynamic organ system which is constantly being remodelled. These processes involve the coordinated effort of osteoblasts and osteoclasts (4). Together, these cell functions ensure healthy bones, giving strength and rigidity to the skeletal system. Osteoblasts are responsible for the deposition of the bone matrix and are thought to facilitate its calcification and mineralization. In contrast, osteoclasts drive the resorption of bone by acidification and the release of lysosomal enzymes, and these cells also produce bone resorption the secretion of MMP-9 (4, 5). Recent studies have explained that *Brucella* spp. can infect and survive within human osteoblasts and that this infection elicits the secretion of proinflammatory cytokines, chemokines and matrix metalloproteinases, that might be involved in the development osteoarticular complications of brucellosis (6, 7).

Matrix metalloproteinases (MMPs) has been implicated in the pathogenesis of infective, cancer and autoimmune diseases. MMPs represent a family of matrix-degrading proteinases with structural similarities. They require coordination of zinc ions at the active site for catalysis. Activity of matrix metalloproteinases is specifically inhibited by the tissue inhibitors of matrix metalloproteinases (TIMPs). To date 20 MMPs have been identified. They can be loosely subdivided on the basis of their substrate specificity into collagenases, gelatinases, stromelysins, matrilysin, macrophage elastase, and four membrane–type MMPs (MT-MMPs). MMP production and activity are highly regulated. Normal tissues do not store MMPs, and constitutive expression is minimal. MMPs are transcriptionally regulated by growth factors, cytokines, and extracellular matrix (ECM) components (8-10). Since MMPs have the capacity to catalyze the degradation of structural ECM proteins, it has been tempting to speculate that their main role is physiological tissue remodelling during development, growth, uterine cycling, postpartum involutio, and wound repair (10). Exuberant expression of MMPs can cause tissue damage, and has been associated with a variety of destructive diseases, including atherosclerotic plaque rupture, aortic aneurysms, tumour progression and arthritis (10). Focus on this family of proteases is particularly emphasized in two major arthritis in humans, osteoarthritis and rheumatoid arthritis (11, 12). Although these forms of arthritis are different in terms of origin, they share the destruction mechanisms of the articular cartilage by proteinases. In human osteoarthritis, many MMPs are expressed in articular cartilage. The immunohistochemical expression levels of MMPs in chondrocytes are reported to correlate directly with the histological destruction score of the articular cartilage (12).

The present study deals with the usefulness and importance of detection matrix metalloproteinases in the diagnosis of human brucellosis.

Materials and methods

Patient data

This study included 60 brucellosis patients and 30 control examinees. The patients were divided into two subgroups: 30 patients with complications and 30 patients without complications of brucellosis. The average age of

patients was 49.9±14.2 years (range 15-81). Among the patients there were 39 (66%) males and 21 (34%) females. All patients were treated at the Clinic for Infectious Diseases, Clinical Centre University of Sarajevo. The average age of the control group of examinees was 36±52.5 years of life, ranging from 18 to 55. There were 26 (86.6%) males and 4 (13.4%) females. All laboratory testing for brucellosis was performed at the Institute for Clinical Microbiology of the Institute for Immunology, Clinical Centre University of Sarajevo. The criterion for inclusion in the study was the etiological confirmation of diagnosis by the relevant laboratory tests. Criteria for exclusion were other inflammatory diseases, autoimmune and malignant diseases. The disease was diagnosed by positive blood culture results and/or by positive relevant serological test results (ELISA, Rose-Bengal latex agglutination). The medical histories of 60 brucellosis patients were analysed. Patient data demonstrated that in order to assess morphological changes in the osteoarticular system, conventional radiological methods had been used (standard radiography-X-ray, computerized tomography-CT and magnetic resonance imaging-MRI).

Serological tests

For serology, blood samples of patients were examined on the first day of hospitalization at the Clinic for Infectious Diseases, Clinical Centre University of Sarajevo. Blood samples were centrifuged and serum was stored in refrigerators at -80 ºC until needed. Serum was evaluated using the Rose-Bengal test and ELISA (IgM and IgG). The Rose-Bengal latex agglutination test was performed according to the standard procedures. Undiluted serum samples (30μL) were mixed with an equal volume of Rose Bengal slide screening test antigen (bio Merioux, Marcy L Etoile/France). The results were rated negative when agglutination was absent and 1+ to 4+ positive according to the strength of the agglutination. Brucella IgM and IgG enzyme-linked immunosorbent assays (ELISAs) were performed and evaluated according to the kit procedure (Genzyme Virotech GmbH, Germany). The test results were read automatically by a BEP 2000-Behring ELISA processor.

Matrix metalloproteinases serum levels were quantified by sandwich ELISA (enzyme-linked immunosorbent assay) using paired MMP-specific monoclonal antibodies, according to the manufacturer's instructions (R&D Systems, Inc., Minneapolis, USA). The test results were read automatically by a BIOTEK ELX50 ELISA processor on 450/620nm. We converted receiving values into pg/ml using the program MASTERPLEX 2010.

Statistical analysis

For evaluation of the results, standard statistical methods were used. An analysis of the normality of the continuous variables was performed with the Kolmogorov-Smirnov test. The test showed that all variables satisfied the characteristics of normal distribution. A comparison of the categorical and continuous variables between the groups was performed using the chi-square test and one-way variance analysis (ANOVA). Correlation between investigated variable was found using Pearson's coefficient linear correlation. Statistical significance was defined at $p<0.05$. Statistical analysis was performed using the statistical package IBM Statistics SPSS V19.0.

Ethical principles

The ethical principles outlined in the World Medical Association Helsinki Declaration were applied in this study.

Results

The investigation involved three groups: 30 patients with complications, 30 patients without complications of brucellosis and 30 in a control group of healthy examinees. Patients had different forms of brucellar complications. Osteoarticular complications were dominant (n=21/30; 70%). The most common form of osteoarticular complication was peripheral arthritis (n=10/21; 47.61%), followed by spondylodiscitis (n=9/21; 42.85%) and sacroilitis (n=4/21; 19.04%). Some patients had manifestations on two segments of the bone-joint system (Figure 1).

The time between onset of symptoms and diagnosis of osteoarticular complications was 7.6±5.4 weeks. The length of diagnostic time was different for different forms of osteoarticular complications. We detected a correlation between the length of diagnostic time and different forms of osteoarticular complications. Nearly twice the length of time was necessary to define the diagnosis of spondylodiscitis (113 days) in relation to arthritis (56 days) and sacroilitis (64 days).

Analysis of the serum level of MMP-1, revealed that in patients with complications it was the highest at 9.45; in patients without complications it was 3.78 and in the control examinees it was the lowest at 3.62, with statistically significant differences between the groups (p=0.001) (Table 1). Serum levels of MMP-9 in patients with complications were the highest at 105.66; in patients without complications they were at 64.67, and in the control examinees they were the lowest at 37.32, with statistically significant differences between the groups (p=0.001) (Table 2). The serum level of MMP-13 in patients with complications was the highest at 138.86; in patients without complications it was 64.85; and in the control examinees it was the lowest at 29.55, with statistically significant differences between the groups (p=0.001) (Table 3). Pearson's coefficient of correlation showed a statistically significant positive correlation between levels of tested matrix metalloproteinases and the development of complications in human brucellosis (p=0.001).

We analysed the correlation between the length of diagnostic time and serum levels of MMPs (MMP-1, MMP-9, MMP-13). MMP-9 and especially MMP-13 showed a correlation with the length of diagnostic time (Figure 2).

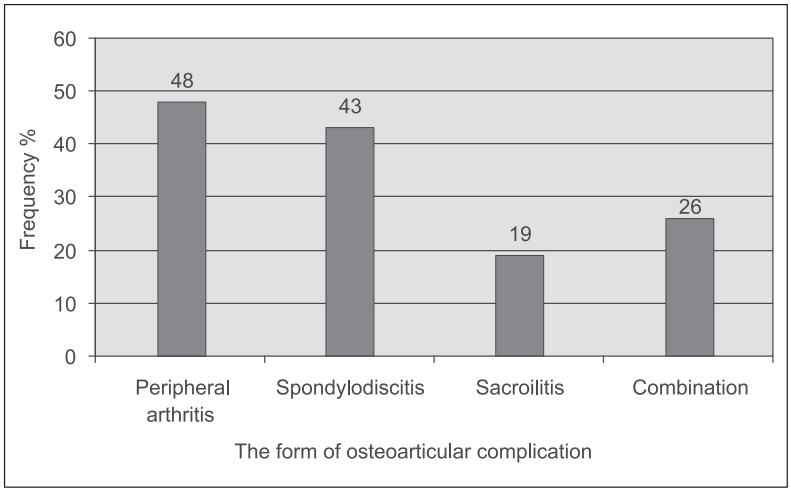

Figure 1 The most common forms of osteoarticular complications in brucellosis.

Table 1 Evaluation of serum level of MMP-1 (pg/ml)

Groups	Serum level of Matrix metalloproteinase1 (pg/ml)				
	AS	SD	SEM	Min.	Max.
Patients with complications (n=30)	9.45	8.16	1.49	1.14	40.96
Patients without complications (n=30)	3.78	2.57	0.47	0.48	8.70
Control (n=30)	3.62	3.11	0.57	0.50	14.07

F=11.964 (results of ANOVA), p=0.001; AS=Arithmetic mean; SD= Standard deviation; SEM=Standard error of the mean; Min=Minimum; Max=Maximum.

Table 2 Evaluation of serum level of MMP-9 (pg/ml)

Groups	Serum level of Matrix metalloproteinase9 (pg/ml)				
	AS	SD	SEM	Min.	Max.
Patients with complications (n=30)	105.66	46.93	8.57	11.24	196.34
Patients without complications (n=30)	64.67	25.66	4.68	19.64	112.89
Control (n=30)	37.32	0.99	0.18	35.57	38.77

F=37.233 (results of ANOVA), p=0.001; AS=Arithmetic mean; SD=Standard deviation; SEM=Standard error of the mean; Min=Minimum; Max=Maximum.

Table 3 Evaluation of serum level of MMP-13 (pg/ml)

Groups	Serum level of Matrix metalloproteinase13 (pg/ml)				
	AS	SD	SEM	Min.	Max.
Patients with complications (n=30)	138.86	97.99	17.89	47.99	576.92
Patients without complications (n=30)	64.85	36.74	6.71	29.06	183.51
Control (n=30)	29.55	0.00	0.00	29.56	29.56

F=25.572 (results of ANOVA), p=0.001; AS=Arithmetic mean; SD=Standard deviation; SEM=Standard error of the mean; Min=Minimum; Max=Maximum.

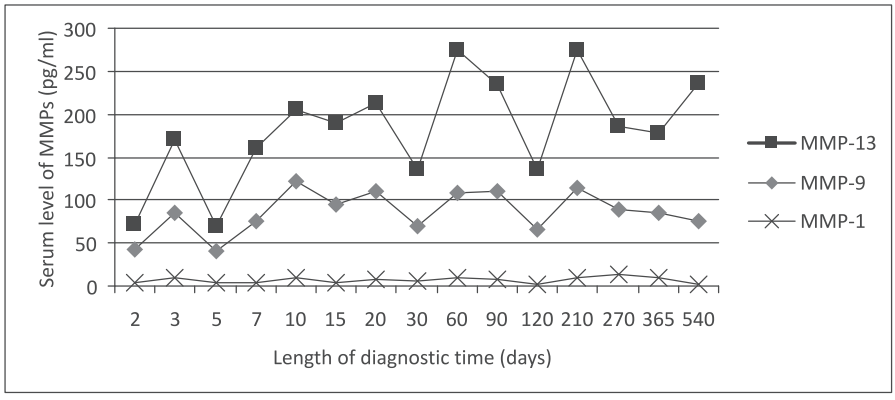

Figure 2 Correlation between the length of diagnostic time and serum level of MMPs.

Discussion

Brucellosis is a prevalent disease in humans and animals in our country. The clinical features and presentations of human brucellosis resemble various infectious, autoimmune or neoplastic processes. Diagnosis of brucellosis in this country without any ex-

perience with this kind of infection, may be very difficult. Early diagnosis of brucellosis and adequate antibiotic therapy have crucial importance for patients, especially for protection from the development of complications. Osteoarticular complications are the most common, and present in the form of spondylodiscitis, sacroilitis, arthritis, tenosynovitis and osteomyelitis (3).

In the present study, osteoarticular complications were dominant (n=21/30; 70%). The most common form of osteoarticular complication was peripheral arthritis, followed by spondylodiscitis and sacroilitis. We detected a correlation between the length of diagnostic time and different forms of osteoarticular complications. Nearly twice the length of time was necessary to define the diagnosis of spondylodiscitis in relation to arthritis and sacroilitis. Bosilkovski et al. (13) in a study in the Republic of Macedonia reported similar results, 59.2% patients had osteoarticular complications. Recent studies in hospitals in various parts of the world have reported similar results (14-19).

The diagnosis of muscular and skeletal system involvement in brucellosis is based on the patient's history, combined with physical examination and imaging methods, of which radiography is the method used most widely. Radiography is the initial means of evaluation of osteoarticular involvement, although its lack of sensitivity in the early stages must be considered. In the early and acute stages, diagnosis of osteoarticular involvement can be difficult because radiography has limited capacity when no changes are present in the bones. Standard radiography showed a low level of sensitivity (32.2%), particularly in the acute phase, due to its inability to differentiate inflammatory and degenerative changes (19). Other techniques that are used widely for imaging osteoarticular involvement are bone scanning, computerised tomography and magnetic resonance imaging (20-22). Bone scintigraphy has been shown as a sensitive method for detecting bone lesions of brucellosis throughout the body. However, its specificity is low (20). Moreover, bone scans do not detect soft tissue infection (20). This is a problem in diseases such as brucellosis, that have both osteoarticular and soft tissue-related complications. Magnetic resonance imaging was a more sensitive method in brucellar osteoarticular changes (21, 22).

Recent studies have shown that brucellar arthritis is frequently destructive, with associated osteopenia and cartilage damage (13-19). However, the pathogenesis of development pathologic changes has not been explained.

Based on the results obtained in the present study, we hypothesize that matrix metalloproteinases may harm osteoblast function, contributing to bone and joint destruction observed in patients with brucellar osteoarticular complications. The results of our study revealed that serum levels of MMPs (MMP-1, MMP-9, MMP-13) in patients with complications were the highest; in patients without complications they were lower and in the control examinees the lowest, with statistically significant differences between the groups (p=0.001). Pearson's coefficient of correlation showed a statistically significant positive correlation between levels of tested matrix metalloproteinases and development of complications in human brucellosis (p=0.001). The expression of MMPs in the serum samples correlates with the parameters of arthritis activity, such as erythrocyte sedimentation rate and C-reactive protein. Also, their degree of expression in the serum samples correlates with the results of conventional radiological methods (standard radiography-X-ray, computerized tomography-CT and magnetic resonance imaging-MRI). Measurement the concentration of metalloproteinases in the serum is non-invasive, easy to perform, relatively inexpensive, and might be a promising

procedure for evaluation of osteoarticular complications. Also, it might be a promising procedure for monitoring the efficiency of therapies in human brucellosis.

Results of our study showed that serum levels of MMP-13 dominated in all patients with osteoarticular complications. Takaishi H. et al. (12) in their study explained the role of MMP-13 in joint diseases. The study concluded that MMP-13 was expressed by chondrocytes and synovial cells in osteoarthritis and rheumatoid arthritis, and plays a critical role in cartilage destruction. MMP-13 serum levels are useful for predicting joint destruction, and monitoring therapies.

The role of MMPs in immunopathogenesis infective and autoimmune osteoarticular diseases has been investigated over the last two decades (17, 18). In patients with inflammatory arthritis gelatinase (MMP-2, MMP-9) are expressed in the synovial membrane, and have been implicated in synovial tissue invasion into the adjacent cartilage and bone. It has been hypothesized that an imbalance between the activators and inhibitors of gelatinases results in higher levels of activity, enhanced local proteolysis, and bone erosion. Radiographic erosions are characteristic. Patients with radiographic erosions had significantly higher levels of active MMP-2 and MMP-9 (17, 18).

Although the clinical aspects of osteoarticular complications in human brucellosis have been described widely (13-19), their immunopathogenesis has been only partially described (6, 7). Wallach JC et al. (23) described a case of prepatellar bursitis in a man with chronic brucellosis. In this case report a high level of proinflammatory cytokines was detected in the synovial fluid. Also, by zymographic analysis the presence of MMP-9 was detected in the synovial fluid of a patient with bursitis. These findings suggest the role of increased local levels of proinflammatory cytokines and gelatinases in the inflammatory manifestations of brucellar bursitis. Delpino MV et al. (24) in an *in vitro* study, described the proinflammatory response of human osteoblast cell lines and osteoblast-monocyte interaction upon infection with *Brucella* spp. The study concluded that osteoblasts play an important role in the pathogenesis of osteoarticular complications in human brucellosis by production of MMPs (MMP-2, MMP-9) and proinflammatory cytokines.

To our knowledge, there are no reports on the ability of *Brucella* spp. to infect human osteoblasts, *in vivo*. This may be explained in part by ethical restrictions, since a biopsy of the affected bone may only be justified in very select cases. Studies, *in vivo*, are important to confirm many emerging and fascinating properties of MMPs.

The results of the present study point out the important role of matrix metalloproteinases in the development of osteoarticular brucellosis. This new knowledge contributes to a better understanding of the osteoarticular pathology of to human brucellosis.

A large number of different tests have been used for serological diagnosis of brucellosis, thus demonstrating the lack of an ideal technique. The Rose Bengal test is ideal for screening patients. ELISA is the method of choice for diagnosis of the chronic disease and relapses. Detection of matrix metalloproteinases in the serum is important for assessment of the disease activity and in predicting development of complications of brucellosis. The correlation between serum levels of MMPs and the results of conventional radiological methods shows the importance of detection of MMPs in the diagnostics of osteoarticular complications of brucellosis. Conventional radiological methods are not useful in determining the outcome of brucellar osteoarticular involvement, because abnormal uptake persists for a long period. Serum levels of MMPs decrease very quickly after adequate antibiotic

therapy, thus demonstrating that they are a reliable technique for monitoring therapies.

Conclusion

This study clearly showed the diagnostic value and importance of detection of matrix metalloproteinases in human brucellosis. Measurement of the concentration of metalloproteinases in the serum is non-invasive, easy to perform, relatively fast, and might be a promising procedure for determining the outcome of brucellar osteoarticular involvement. Although increased levels of MMP-1, MMP-9 and MMP-13 are not specific and do not provide a definite clinical diagnosis, they can be used as a biochemical indicator of development of complications, when evaluated in combination with conventional radiological methods. Serum levels of MMPs decrease very quickly after adequate antibiotic therapy, thus demonstrating that they are a reliable technique for monitoring efficiency of therapies.

What is already known on this topic

- *Matrix metalloproteinases has been implicated in the pathogenesis of infective, cancer and autoimmune diseases.*
- *MMPs production and activity are highly regulated.*
- *Normal tissues do not store MMPs, and constitutive expression is minimal.*
- *Exuberant expression of MMPs can cause tissue damage, and has been associated with a variety of destructive diseases, including atherosclerotic plaque rupture, aortic aneurysms, tumour progression and arthritis.*

What this study adds

- *This investigation showed the diagnostic value and importance of detection of matrix metalloproteinases in human brucellosis.*
- *Measurement of the concentration of metalloproteinases in the serum is non-invasive, easy to perform, relatively fast, and might be a promising procedure for determining the outcome of brucellar osteoarticular involvement.*
- *Serum levels of MMPs decrease very quickly after adequate antibiotic therapy, thus demonstrating that they are a reliable technique for monitoring the efficiency of therapies.*

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

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

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Original article

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Methicillin-resistant Staphylococcus aureus in North-east Croatia

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Objective. The aim of this 5-year study was to determine the frequency and antibiotic susceptibility of methicillin-resistant *Staphylococcus aureus (*MRSA)-related infections at Osijek Clinical Hospital. **Materials and methods.** A total of 1987 staphylococci-infected clinical isolates were collected and analysed at the Microbiology Department of the Public Health Institute of Osijek-Baranja County. **Results.** Between 2008 and 2012, the average rate of MRSA-related infections in staphylococci-infected patients was 27.4%. The proportion of MRSA-related infections on all *Staphylococcus aureus (S. aureus)* isolates from clinical specimens showed a decreasing trend, from 32.6% in 2008 to 25.5% in 2012. MRSA-related infections were mostly detected in wound swabs (50.6%) and aspirates (28.8%) of patients hospitalized in the surgical (49.8%) and intensive care units (27.9%). MRSA-related infection showed an increase compared to *S. aureus*-infections in samples of wounds and aspirates in 2011 and 2012 (57.9%/34.9% and 35.2%/16.3%, respectively). The majority of strains of MRSA-related infections were resistant to several antibiotics, including erythromycin and clindamycin, where susceptibility were less than 10%. All MRSA isolates were susceptible to vancomycin, teicoplanin and linezolid. Therefore, antibiotic therapies for MRSA infections include vancomycin, teicoplanin and linezolid, but microbiological diagnostics need to be performed in order to know when the use of glycopeptides and oxazolidinones is indicated. **Conclusion.** Our results suggest that appropriate prevention measures, combined with the more rational use of antibiotics are crucial to reduce the spread of MRSA-related infection in healthcare settings. Further monitoring is necessary of the incidence and antibiotic susceptibility of MRSA-related infections in our community.

Introduction

The bacterium *Staphylococcus aureus* (*S. aureus*) is a serious opportunistic human pathogen (1). It belongs to normal bacterial flora and is often detected in the nasal vestibule and on other body surfaces in 20%-30% of humans. *S. aureus* synthesizes more than 30 virulence factors that may cause numerous clinical symptoms. In addition to local skin infection, a typical sign of a staphylococcal infection, it also leads to abscesses, osteomyelitis, pneumonia, sepsis, endocarditis, and post-operative infections. More-

over, *S. aureus* toxins may result in poisoning and toxic shock (2, 3).

The remarkable ability of *S. aureus* to develop antibiotic resistance makes it a worldwide problem. Through the process of natural selection (mostly transmission), methicillin-resistant *S. aureus* (MRSA) has developed resistance to macrolides, linkosamides and aminoglycosides and an entire class of antibiotics called beta-lactams (including the penicillins and the cephalosporins). Staphylococcal strains that are susceptible to these antibiotics are classified as methicillin-sensitive *S. aureus* (MSSA). The first MRSA was isolated in Great Britain in 1961, then in the USA in 1968, which was followed by its detection in Japan, Europe and Australia. MRSA has been one of the most common causes of healthcare-associated infections. It has been estimated that MRSA infects 171,200 people in the EU, Island and Norway annually, leading to 44% of all cases of health-care associated infections (4-7). The frequency of MRSA-related infections has slowed down in the West, but in the Northeast, Midwest and South of the USA MRSA-related infections have shown an increase. *S. aureus*-related infections have been shown to be increasing in the Northeast, Midwest, South and in the West (8).

There are two types of MRSA infections in human hosts: hospital-acquired MRSA (HA-MRSA) and community acquired MRSA (CA-MRSA), and there is one type of MRSA infection in livestock: livestock-associated MRSA (LA-MRSA). HA-MRSA is a secondary infection, which patients pick up in hospital. CA-MRSA infection is an infection which develops outside the hospital, through exposure to a carrier or contaminated surface in the wider community. LA-MRSA infections colonize livestock, including pigs, cattle and poultry (6, 9, 10). Some studies have suggested that previous hospitalization is associated with CA-MRSA (8, 11).

MRSA spreads easily in hospitals, usually through the hands of health workers or contaminated objects. The colonization of health workers with MRSA is especially dangerous. Risk factors that contribute to MRSA spread are subtherapeutic doses or the overuse of antibiotics, long-term hospital stay and intravascular catheterizations in intensive care units (ICUs). The potential sites for MRSA infection in hospital patients are open wounds, intravenous catheters and the respiratory and urinary tracts (4, 12-14).

MRSA infections in hospital settings have been a serious issue across the world. MRSA infections prolong hospital stay and excessive antibiotic usage which raise the total cost of hospitalization. Hand hygiene, decontamination, and contact isolation of colonized and infected patients are the most important prevention measures. MRSA strains can be detected in clinical specimens using standard microbiological procedures, following the guidelines set by the 2011 European Committee on Antimicrobial Sensitivity Testing (EUCAST). MRSA is a multidrug resistant isolate, causing infections that are difficult to treat. In treatment of MRSA-related infection vancomycin, linezolid and tigecyclin (15-17) may be used.

To our knowledge, this is the first study on MRSA-related infection frequency and antibiotic resistance in hospital patients from north-east Croatia. This was a 5-year study that analysed 1987 staphylococci-infected clinical specimens collected at Osijek Clinical Hospital.

Materials and methods

Samples

This study was performed between January 2008 and December 2012, and included 1987 staphylococci-infected isolates. All isolates were collected at the Osijek Clinical Hospital Centre. The presence of Staphylococcus

was analysed in clinical samples: aspirates, catheters, wounds, blood, liquor and urine, which are collected on the surgical, internal medicine, paediatric, infectious diseases and ICU wards. All samples were analysed at the Microbiology Department of the Institute of Public Health of the Osijek-Baranja County. Only one sample per patient was included in the study.

Laboratory methods

Samples were cultivated on blood agar plates and incubated at 37°C for 18-24 hours in a microbiology laboratory. The presence of *Staphylococcus* was confirmed by the microscopic analysis of Gram-stained samples and a catalase test. In order to distinguish between *S. aureus* and coagulase-negative staphylococci (CoNS) we used deoxyribonuclease (DNase), coagulase and latex agglutination tests (Bio-Rad, Latex agglutination test for the identification of *Staphylococcus aureus*, Version 2012.). MRSA was determined from its resistance to cefoxitin by the disk diffusion technique. Cefoxitin resistant MRSA was confirmed by a fast latex agglutination test that detects penicillin-bound proteins (Oxoid, Test kit for the detection of PBP 2′, Version 2012.). MRSA isolates that were PBP 2′ agglutination-negative were further verified by an automatic identification system VITEK (BioMérieux, Vitek 2, Version 2008.).

The antibiotic susceptibility of MRSA was analysed to the following antimicrobial drugs: ciprofloxacin (5 μg), gentamycin (10 μg), clindamycin (2 μg), erythromycin (15 μg), netilmycin (10 μg), linezolid (10 μg), rifampicin (5 μg), teicoplanin (30 μg), vancomycin (5 μg) and sulfamethoxazoletrimethoprim (1.25/23.75 μg). EUCAST guidelines were followed for the susceptibility and result analysis.

Methicillin resistance was evaluated by a cefoxitin disk diffusion test. Müller-Hinton agar was covered with a bacterial suspension to the density of the McFarland 0.5 standard and incubated for 18-24 hours in air at 37°C. A bacterial isolate was considered to be resistant to all beta-lactam antibiotics if the size of its inhibition zone was <22 mm. For the strains with border values for inhibition zones diameters for cefoxitin the minimal inhibitory concentration (MIC) was determined. Isolates with values >4 mg/l were considered to be MRSA-positive (15, 18, 19).

Ethics statement

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

Statistical analysis

The χ^2 and Fisher's exact test, as appropriate, were used to compare percentage data (*i.e.,* distribution between *S. aureus*-related infections and MRSA-related infections in different hospital units by years; distribution between *S. aureus*-related infections and MRSA-related infections in different clinical samples). 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 Statistica 8.0 (StatSoft) and Microsoft Office Excel 2007/2010 (Microsoft).

Results

The number of *S. aureus*-related infections and MRSA-related infections from aspirates, wounds, catheters, blood, urine and liquor samples collected at the Osijek Clinical Hospital Centre between 2008 and 2012 is presented in Table 1.

Table 1 Proportion of *S. aureus*-related infections and MRSA-related infections in different clinical samples per year

Year	Infection	Different clinical samples						Total
		Aspirates	Wounds	Catheters	Blood	Urine	Liquor	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
2008	*S. aureus*	54 (21.7)	108 (43.4)	14 (5.6)	46 (18.5)	19 (7.6)	8 (3.2)	249
	MRSA	32 (26.6)	67 (55.8)	3 (2.5)	11 (9.3)	4 (3.3)	3 (2.5)	120
2009	*S. aureus*	76 (24)	118 (37.3)	34 (10.8)	63 (19.9)	14 (4.5)	11 (3.5)	316
	MRSA	38 (28.1)	67 (49.6)	3 (2.2)	16 (11.9)	2 (1.5)	9 (6.7)	135
2010	*S. aureus*	69 (20.8)	123 (37.2)	39 (11.8)	72 (21.8)	9 (2.7)	19 (5.7)	331
	MRSA	29 (29.9)	49 (50.5)	3 (3.1)	6 (6.2)	1 (1)	9 (9.3)	97
2011	*S. aureus*	59 (20.2)	102 (34.9)	33 (11.3)	67 (22.9)	13 (4.5)	18 (6.2)	292
	MRSA	26 (25.5)	59 (57.9)	1 (0.9)	8 (7.9)	3 (2.9)	5 (4.9)	102
2012	*S. aureus*	42 (16.3)	98 (38.1)	29 (11.3)	56 (21.8)	20 (7.8)	12 (4.7)	257
	MRSA	31 (35.2)	32 (36.4)	4 (4.5)	13 (14.8)	6 (6.8)	2 (2.3)	88

S. aureus=Staphylococcus aureus; MRSA=methicillin-resistant *Staphylococcus aureus.*

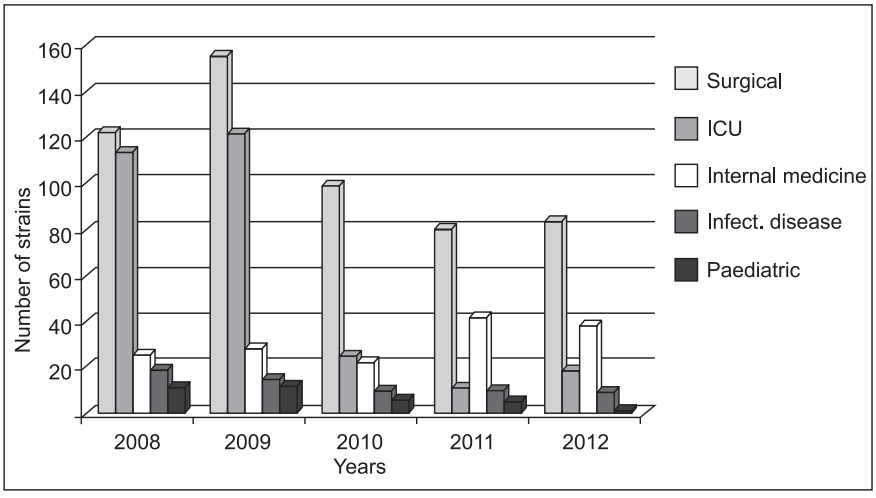

Figure 1 MRSA-related infection distribution by hospital wards.

Out of 1987 staphylococci-infected isolates collected between 2008 and 2012, 542 (27.4%) were MRSA-related infections and 1445 (72.6%) were *S. aureus*-related infections. The annual rate of MRSA-related infections in our hospital showed a slight downward trend, from 32.6% in 2008 to 25.5% in 2012 (χ^2=12.41, p=0.0145). Table 1 shows that the MRSA-related infections showed an increase compared to *S. aureus*-related infections in wound and aspirate samples in 2011 and 2012 (57.9%/34.9% and 35.2%/16.3%, respectively).

Figure 1 shows that isolates from the surgical wardd and ICU had higher rates of MRSA-related infection (49.8% and 27.9%, respectively) than samples from the internal medicine, infectious and paediatric units (12.7%, 6.8%, and 2.8%, respectively). This difference was statistically significant (χ^2=113.46, p<0.0001).

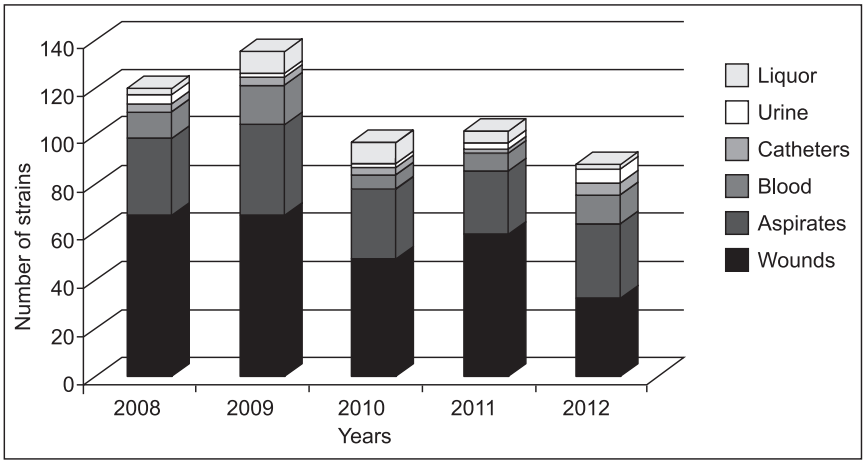

Figure 2 MRSA-related infection distribution by clinical samples.

Table 2 Antibiotic susceptibility of MRSA-related infection isolates

Antimicrobial agent	Number of susceptible MRSA-infection isolates (%) per year				
	2008 (n=120)	2009 (n=135)	2010 (n=97)	2011 (n=102)	2012 (n=88)
	n (%)	n (%)	n (%)	n (%)	n (%)
Ciprofloxacin	2 (1.7)	10 (7.4)	6 (6.2)	6 (5.9)	5 (5.7)
Gentamycin	9 (7.5)	11 (8.1)	7 (7.7)	17 (16.6)	11 (12.5)
Clindamycin	3 (2.5)	9 (6.6)	2 (2.1)	7 (6.7)	1 (1.1)
Erythromycin	3 (2.5)	3 (2.2)	1 (1)	8 (7.8)	4 (4.5)
Netilmycin	119 (99.2)	133 (98.5)	94 (96.9)	91 (89.2)	66 (75)
Linezolid	120 (100)	135 (100)	97 (100)	102 (100)	88 (100)
Rifampicin	115 (95.8)	116 (85.9)	67 (69.1)	90 (88.2)	80 (90.9)
Teicoplanin	120 (100)	135 (100)	97 (100)	102 (100)	88 (100)
Vancomycin	120 (100)	135 (100)	97 (100)	102 (100)	88 (100)
Sulfamethoxazole trimethoprim	92 (76.6)	115 (85.2)	75 (77.3)	81 (79.4)	72 (81.8)

Out of 542 MRSA-related infections samples analysed in this 5 year study, the majority was detected in wound swabs (50.6%) and aspirates (28.8%) (Figure 2).

A significantly lower level of MRSA-related infections was detected in blood (10.0%), urine (2.9%), catheters (2.6%), and liquor (5.1%) samples (χ^2=128.11, p<0.0001).

Table 2 summarizes the susceptibility of 542 MRSA-related infection isolates to several antimicrobial drugs used in the treatment of MRSA infections. All MRSA-related infection strains analysed in this study were susceptible to vancomycin, teicoplanin and linezolid.

In contrast, less than 10% of MRSA-related infection strains were susceptible to erythromycin or clindamycin. Their highest susceptibility to these two antibiotics was detected in 2011 (7.8% and 6.7%, respectively). While the susceptibility of MRSA-related infection strains to netilmycin showed a downward trend, their susceptibility to ciprofloxacin and gentamycin increased (from 1.7% and 7.5% in 2008 to 5.7% and 12.5% in 2012).

Discussion

The overall frequency of MRSA-related infections between 2008 and 2012 at Osijek Clinical Hospital was 27.4%. This rate correlated with the results reported by Mehta et al. (32.0%) but was smaller than those reported by Kuehnert et al., Anupurba et al. and Tiwari et al. (43.2%, 54.8% and 69.1%, respectively) (14, 20-22). MRSA-related infection from blood and liquor samples in 2010 and 2011 was 14.5% and 12.8% which is similar to the results reported from Croatia by Budimir et al. and from the United States of America by Hacek et al. (23, 24). The slight downward trend in the annual frequency of MRSA-related infections at Osijek Clinical Hospital may be explained by the rising awareness of MRSA, more efficient prevention programs and less frequent antibiotic administration.

With a capacity of 1160 beds, Osijek Clinical Hospital is the largest healthcare centre in north-east Croatia. The largest incidence of MRSA-related infections was detected in the surgical ward and the ICU. The latter is a polyvalent unit with 12 beds and ¾ of its patients arrive from surgical units. This rate correlated with the results reported by Joshi et al. (25).

The largest number of MRSA-related infections was detected in wound swabs and aspirates. The high incidence of MRSA-related infections in aspirates is linked to the fact that ICU patients underwent endotracheal intubation. These results correlated with reports from Pakistan and India (4, 21). All MRSA strains detected in this study were susceptible to vancomycin, linezolid and teicoplanin. Vancomycin-sensitive MRSA strains were also reported in studies from Bosnia and Herzegovina, Romania, Ireland, the United Kingdom, India, and Columbia (23, 26-31). However, vancomycin-resistant *S. aureus* (VRSA) strains were discovered in the USA (32, 33).

The majority of our MRSA strains were not susceptible to erythromycin and clindamycin. Moreover, their susceptibility to netilmicin showed a downward trend between 2008 and 2012. On the other hand, their susceptibility to ciprofloxacin and gentamycin increased during this 5-year period. These observations correlate with the results reported by the Committee for Antibiotic Resistance Surveillance in Croatia (Croatian Academy of Medical Sciences).

Conclusion

In conclusion, despite some limitations (the lack of epidemiological evidence about the reason and length of hospital stay), this 5-year study was the first study on MRSA-related infection frequency and antibiotic resistance in hospital patients from north-east Croatia. This study demonstrates that MRSA-related infection is a problem in north-east Croatia. Due to the 100%-efficient susceptibility of MRSA strains in patients at the Osijek Clinical Hospital to vancomycin, linezolid and teicoplanin, these antibiotics should be avoided in therapy. Further monitoring is necessary of the use of antibiotics, incidence of MRSA-related infections and their antibiotic susceptibility. This study can enable epidemiologists to understand the nature of MRSA infections in north-east Croatia.

What is already known on this topic

- *MRSA is one of the most common causes of healthcare-associated infections. The most important MRSA related problem is the development of resistance to antibiotics.*

What this study adds

- *This study shows that regular surveillance of hospital-associated infections and monitoring of their antibiotic sensitivity patterns are required to reduce MRSA-infection frequency in hospital patients from north-east Croatia. Accurate and continuous surveillance of antibiotic resistance combined with the more rational use of antibiotics are crucial for reducing MRSA-related infections.*

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Autors' contributions: Conception and design: TP, MP, DV; Acquisition, analysis and interpretation of data: NR, VA; Drafting the article: ZB, JT; Revising it critically for important intellectual content: PRM, LZS.

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

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National survey of pain clinics in Croatia: Organization and services

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Objective. To analyze organization and therapeutic procedures administered in tertiary outpatient pain clinics in Croatia. **Methods.** Data about organization of pain clinics, its personnel, equipment, continuing medical education, therapeutic procedures, research activities and relations with pharmaceutical industry were collected using questionnaires. **Results.** Twenty-two Croatian pain clinics were included in the study. Most of the pain clinics employ exclusively anesthesiologists and nurses. The most frequently prescribed therapeutic procedures in pain clinics were pharmacotherapy, transcutaneous electrical nerve stimulation, acupuncture and trigger point injections. Almost all pain clinics provide educational material for patients. Most of the pain clinics have regular interactions with pharmaceutical companies. Prescribing decisions were based mostly on information from scientific meetings, research articles and consultations with colleagues. Information sources which are considered to be the gold standard – the systematic reviews of The Cochrane Collaboration – were used less frequently (n=12; 57%) than advertising materials from pharmaceutical companies (n=16; 76%). Few physicians and other pain clinics staff had scientific degrees or academic titles or were involved in a research project. **Conclusion.** The national study about pain clinics in Croatia pointed out that there is room for improvement of their organization and services. Pain clinics should employ health-care professionals with diverse backgrounds. They should offer treatments backed by the highest-level of scientific evidence. Since pain is a major public health issue, pain clinic staff should engage more in research to contribute to the growing field of pain research, to enhance capacities for pain research in Croatia, to incorporate scientific evidence into their daily decision-making and to enable evidence-based practice.

Introduction

Pain is an unpleasant sensory and emotional experience associated with real or potential tissue damage (1). Clinics for pain treatment (i.e. pain clinics) are specialized health care units employing experts in pain management. The main activity of pain clinics is the treatment of patients with acute and chronic pain, education of health care professionals and patients, participation in professional and scientific meetings, participation in the preparation of guidelines and research in the field of pain. Patients with chronic pain have a tendency towards depression, anxiety and social isolation so they require a great level of dedication and continuous care. Many of these pa-

tients require an interdisciplinary approach, which should be offered in pain clinics (2).

The first clinic dedicated to pain management was established by John J. Bonica and Lowel White in 1961 at the University of Washington at Seattle, USA. Dr. Bonica advocated an interdisciplinary approach to the treatment of complex pain disorders. Interdisciplinary approach to pain management includes collaboration of anesthesiologists, neurologists, rehabilitation physicians, psychiatrists and other professionals that address many facets of pain (3). Pain clinics provide a specialised service for patients with more complex and intractable pain problems (4). At the time of the study, Croatia had 22 pain clinics registered with the Croatian Health Insurance Fund (CHIF) (5).

Therapeutic procedures prescribed in pain clinics may include pharmacotherapy, regional anesthesia, epidural analgesia, transcutaneous electrical nerve stimulation (TENS), ultrasound (US), laser treatment, magnetic therapy, acupuncture, trigger point injections and a number of other treatments in the domain of conventional and alternative medicine (6). A recent study conducted at the pain clinic of the University Hospital Split showed that the clinic did not offer an interdisciplinary approach to the pain treatment, and for the majority of non-pharmacological therapies offered in the pain clinic there is no evidence about their effectiveness (7). There are no studies about therapeutic procedures provided by other pain clinics in Croatia, their working conditions and staff, their organization of practice, links with the pharmaceutical industry, or their involvement in education and research.

National studies about the organization and procedures offered at pain clinics are rare in medical literature. For optimal functioning, pain clinics require adequate space and equipment for therapeutic interventions, as well as diverse team of health professionals. However, many pain clinics in Croatia lack adequate space and a multidisciplinary teams that represent current standard in pain treatment, as recommended previously (3). Our previous study conducted in one pain clinic showed that patients were generally satisfied with pain clinic services, but suggested increasing number of staff, a better approach to each patient, and better organization of work (8). However, one of our previous studies also showed that pain clinics offer treatments that are not necessarily evidence-based (7).

The aim of this study was to analyze the organization of tertiary outpatient pain clinics in Croatia and of the therapies they provide. Information gained in this study may provide recommendations for further development of pain clinics for the benefit of patients suffering from pain.

Methods

The study was conducted among head physicians of the 22 tertiary outpatient pain clinics in Croatia in 2013 by using a questionnaire (Appendix 1). The study was approved by the Ethics Committee of the University of Split School of Medicine. An informed consent was obtained by all physicians participating in the study.

Questionnaire

The questionnaire consisted of 34 questions about the organization, personnel and equipment available in a pain clinic, professional training of the staff, therapeutic procedures offered by a pain clinic, research activities conducted in a clinic and relationships with the pharmaceutical industry (Appendix 1). The questionnaire was developed specifically for the purpose of this study.

General questions addressed the year of pain clinic establishment, surface area of the pain clinic, the number of physicians working in the clinic and their specializa-

tion, the number of nurses working in the clinic, availability of other professionals except physicians and nurses, the information whether the pain clinic was registered by the CHIF, availability of electronic patient records, working hours of the pain clinic, the average number of patients per week, procedures for data collection.

In order to obtain information about professional training of the staff, the following data were collected: whether employees of the pain clinics attended continuing medical education (CME) courses and whether they organized lectures for patients. Availability of educational materials for patients was also studied. Physicians were also asked how therapies were chosen and which of the therapeutic procedures of alternative and complementary medicine were offered in the pain clinic.

The following information about research activities in pain clinics were collected: number of physicians with MSc and PhD degree, number of physicians holding an academic degree (assistant professor, associate professor, full professor), and a number of research projects. Scientific output was analyzed from the number of research manuscripts on pain. Frequency and type of contacts with the pharmaceutical industry were also analyzed, as well as funding received from the pharmaceutical industry.

Data analysis

The study did not use any personal patient data. The names of the persons who responded to the questionnaire were known to only two researchers and their names were not recorded or used during the data analysis. The data were entered into an electronic spreadsheet and analyzed by descriptive statistics. Collected data were analyzed using GraphPad Prism software (GraphPad Software Inc., San Diego, CA, USA).

Results

Pain clinics in Croatia

Out of 22 pain clinics in Croatia, 21 participated in the study. Six pain clinics were in Zagreb, 2 were in Rijeka and the rest were distributed in other Croatian towns. Territorial distribution of pain clinics in Croatia

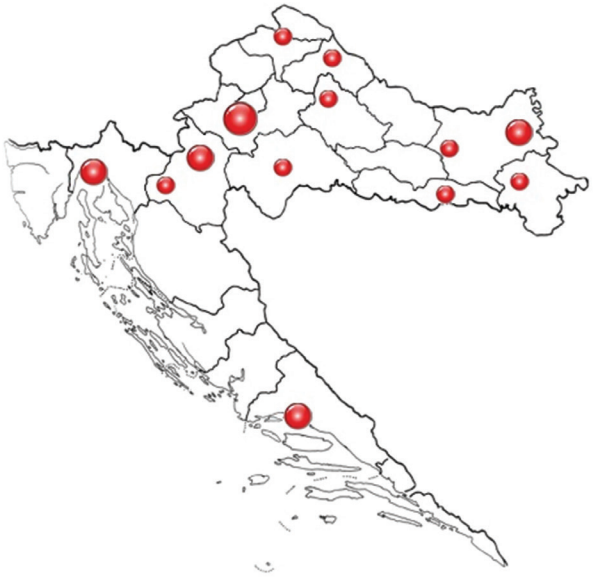

Figure 1 Territorial distribution of pain clinics in Republic of Croatia.

shows that they were mostly located in the continental part of Croatia (Figure 1).

The first Croatian pain clinic was established in Karlovac in 1979, followed by five more that were established before 2000. Pain clinics in Croatia worked for a median of 12 years (range: 3-35). The size of pain clinics varied considerably. The median surface area of the clinics was 25 m^2 (range: 9-150 m^2). The Clinic for Anesthesiology, Reanimation and Intensive Care Hospital Centre Zagreb (Jordanovac) had the smallest area of 9 m^2, while the pain clinic in Hospital Koprivnica had the largest area of 150 m^2.

The average number of patients visiting pain clinics per week was 81.7 (range: 10-320). The average number of patients who visited clinics for the first time was 14 per week (range: 2-30). Information about therapeutic procedures conducted in the clinics and the most common diagnoses could be easily retrieved in 13 (62%) clinics that used electronic patient records.

Pain clinic personnel

Pain clinics mostly employed physicians, anesthesiologists and nurses. Four (19%) pain clinics employed experts that were not physicians and nurses: General Hospital Koprivnica (a psychiatrist, a psychologist, a physiotherapist and, when needed, a priest), Clinical hospital Merkur (two neurologists and a psychologist), Clinical Hospital Osijek (an administrator) and Clinical hospital center "Sestre milosrdnice" (a neurologist, a physiotherapist, a psychiatrist, when needed). The median number of anesthesiologists per pain clinic was 3.5 (range: 1-7). The median number of nurses was 1 (range: 1-6).

Organization of pain clinics

There were 18 (86%) pain clinics with a CHIF contract. All pain clinics used computers for typing and printing patient records. Most of the pain clinics had easily accessible archives of treated patients (n=20; 95 %), with 16 (76%) of them using electronic archives. A total of 15 (71%) clinics were open every working day. The median of weekly working hours in pain clinics was 35 (range: 10-42).

Therapeutic procedures available in the clinics

All pain clinics prescribed pharmacotherapy. Some of the clinics also provided other therapies, most commonly TENS, acupuncture and injection of trigger points (Table 1).

Table 1 Therapies used in pain clinics

Type of treatment	n (%)
Pharmacotherapy	21 (100)
TENS	19 (90)
Acupuncture	17 (81)
Injection of trigger points	16 (76)
Magnetotherapy	12 (57)
Epidural analgesia	11 (52)
Regional blocks	10 (48)
Ultrasound	10 (48)
Epidural catheter	9 (43)
Intrathecal injections	4 (19)
Subcutaneous administration of drugs (using pumps)	2 (10)

TENS=Transcutaneous electrical nerve stimulation.

When asked about complementary therapies available to patients, 7 pain clinics indicated that they offered some complementary therapies, listing the following interventions: laser acupuncture, phytotherapy, minimally invasive treatment of pain under control of fluoroscope in the operating room, VIP Bioptron lamp, psychotherapy based on the analysis of anxiety and depression test, intravenous application of analgesics, chiropractic services, group psychotherapy and phytotherapy.

Educational activities

All clinics engaged in educational activities for their personnel or patients. Educational materials for patients were available in all clinics, prepared either by pharmaceutical companies, Croatian Association for the Treatment of Pain or employees of the clinics. Less than half of the clinics organized CME courses (Table 2).

Table 2 Type of educational activities in the pain clinics

Educational activities	n (%)
Promotional materials for patients	20 (96)
Promotional materials for patients created by the pharmaceutical industry	20 (96)
Promotional materials for patients created by Croatian Association for the treatment of pain or other medical organization	13 (62)
Courses for patients organized by pain clinic personnel	12 (57)
Continuing medical education courses organized by pain clinic personnel	10 (48)
Promotional materials for patients created by pain clinic personnel	8 (38)

Selecting prescription drugs

When prescribing pharmacological interventions in pain clinics, most of the physicians indicated that they based their prescription choice on knowledge from scientific meetings (n=20; 96%), research papers (n=20; 96%) and consultations with colleagues (n=20; 96%). Information sources which are considered the gold standard – systematic reviews of The Cochrane Collaboration – were used less frequently (n=12; 57%) than advertising materials of pharmaceutical companies (n=16; 76%) for making prescribing decisions.

Contacts with pharmaceutical companies

Physicians at the heads of the Croatian pain clinics indicated different types of interactions with pharmaceutical companies, including receiving visits from pharmaceutical industry representatives and getting information about the products and receiving funding for various purposes (Table 3).

Table 3 Interaction with pharmaceutical companies

Type of contact with pharmaceutical companies	n (%)
Dialogue with representatives and getting information material about products	20 (96)
Funding of scientific meetings organized by the employees of pain clinics	9 (43)
Funding of CME courses	11 (53)
Financing travel expenses and registration fees for scientific meetings	17 (82)
Financing travel expenses and registration fees for CME courses	14 (67)
Presentation (dinners, meetings with company representatives)	3 (14)
Donations of devices used in the treatment and diagnosis	3 (14)
Donations to purchase devices that are not used in the treatment and diagnosis	0 (0)

CME=Continuing medical education.

Amount of money spent by pharmaceutical companies for the listed activities annually was less than 1.630 USD in 8 (39%) pain clinics, between 1.630 USD and 4.890 USD in 7 (35%) pain clinics and between 4.890 USD and 11.420 USD in 1 (4%) clinic. Head of one clinic indicated that they did not receive any funding from pharmaceutical companies, while one indicated that it was not known how much pharmaceutical companies annually spent for the listed activities.

Scientific profile of physicians working in pain clinics

Very few physicians and other employees of pain clinics had scientific degrees and academic titles. Median number of physicians with MSc degree was 1 (range 0-3); median number of PhD degrees was 0.6 (range: 0-2), the median number of physicians with

academic titles was 0.4 (range: 0-1), while among non-physician employees median number of those with academic titles was 1.1 (range: 0-4).

Scientific activities in pain clinics

Four (20%) pain clinics had employees conducting a research project. In 12 (57%) pain clinics data collected from patients were used for research purposes. Range of number of scientific papers published by employees of pain clinics in the last 5 years indexed in *Current Contents* (CC) was 0-5. A number of scientific papers published by the employees in the last 5 years indexed in *Index Medicus* ranged from 0 to18. A number of scientific papers about pain published in CC and in journals from pain research area ranged from 0 to 3. Number of scientific papers about pain published by employees in the last five years in *Index Medicus* and in journals from pain research area ranged from 0 to 10. Data about the most common diagnoses in the analyzed pain clinics were not presented hereby because they were answered by a very few physicians.

Discussion

Geographical distribution of pain clinics in Croatia showed that most of them were located in the continental part of the country. This clustering of clinics in the central part of Croatia puts the rest of the country at a disadvantage regarding the ease of access to pain clinics. The first pain clinic was founded in 1979, while the majority of Croatian pain clinics were founded after 2000. Pain clinics mostly employ physicians and nurses. They have electronic patient records and most of them work every weekday. All clinics prescribe pharmacotherapy, but also provide a range of other services. Nearly all clinics maintain regular contacts with pharmaceutical companies regarding drug information and many of them receive funding for scientific and professional training. Most of the pain clinics have educational materials for patients. Very few employees of pain clinics hold scientific and academic titles, and their research activities were modest.

This study showed that pain clinics in Croatia are staffed almost exclusively with physicians and nurses. However, an indication that this is changing came from the 3rd Croatian Congress on pain therapy in Osijek, Croatia in May 2014. The head of the pain clinic from Osijek introduced the first multidisciplinary program for the treatment of chronic pain in Croatia. The program started recently and it would be desirable for other pain clinics to follow the example set by the Osijek pain clinic (9). Space areas of the pain clinics indicate that they do not have the same spatial conditions and that some very small pain clinics may not have adequate conditions for delivering multifaceted patient-carer interaction.

Information about therapeutic procedures and common diagnoses in pain clinics are valuable for planning health care services and improvement of pain management facilities (10). In all pain clinics in Croatia, pharmacotherapy was the basic modality of pain management, same as in other pain clinics in the world. Despite the availability of many drugs for pain treatment, pain control is not optimal due to the use of ineffective drugs or prescribing low doses (11). It has been recommended that a combination of analgesics with non-pharmacological treatment should be used for pain management (for example a combination of pregabalin and TENS) (12). The results of this study indicate that, in addition to pharmacotherapy, Croatian pain clinics also frequently prescribe TENS, acupuncture and injection of trigger points. Pain clinics in the world are increasingly using TENS for musculoskeletal and neuropathic pain (13). However, evidence supporting the use of TENS for

chronic pain is scarce. A Cochrane systematic review on TENS for low back pain (LBP) found conflicting evidence regarding the benefits of TENS for chronic LBP, which does not support the use of TENS in the routine management of chronic LBP (14). There was insufficient evidence about the effectiveness of TENS for cancer-related pain (15). No randomized controlled trials were found about TENS for phantom pain and stump pain in adults (16). Conflicting evidence was found for TENS regarding pain outcomes in rheumatoid arthritis (17).

Acupuncture was offered in most Croatian pain clinics. Prescription of acupuncture in the United States is slowly increasing and it is prescribed as a supplement or replacement method for the treatment of chronic pain syndromes (18). The effectiveness of acupuncture for treatment of chronic pain was analyzed in a series of systematic reviews. The evidence of moderate or low quality shows that compared with standard therapy or no therapy, acupuncture relieves pain in patients with fibromyalgia (19). Some specific evidence suggests that the acupuncture may be effective for pain relief during labor and dysmenorrhea, although additional research is required for definitive confirmation (6, 20). There is no evidence that supports the effectiveness of acupuncture for irritable bowel syndrome, endometriosis or cancer pain (21-23). Therefore, it can be concluded that there is conflicting evidence on the effectiveness of acupuncture for pain relief and further clinical trials on this subject are necessary.

Magnetotherapy was offered by more than half of the pain clinics, even though evidence about its effectiveness for pain management is also scarce (24). The same can be said for therapeutic ultrasound for pain treatment, for which recent systematic reviews have shown no evidence or low-quality evidence for its efficacy in multiple conditions (24-27).

Other non-pharmacological methods for pain treatment were offered in several Croatian pain clinics. When pain clinic representatives were asked about complementary therapies used in their pain clinics, they listed several interventions that belonged to the conventional medicine, such as psychotherapy or intravenous application of analgesics. This indicates that not all physicians contacted were aware of the concept of complementary therapies.

There are several international manuscripts about the organization and delivery of pain services that could be used as a guidance for improving pain management (28-32). Educational activities in most pain clinics in Croatia focus on providing educational materials for patients developed by pharmaceutical companies, and less frequently on educational materials developed by the Croatian Association for the Treatment of Pain or employees of the clinics. There are educational activities that have been proven as effective for pain relief and pain clinics should consider using such interventions (33).

Most of the contacted physicians in pain clinics in Croatia prescribed medications based on information from scientific conferences, research papers, consultations with colleagues and educational materials from pharmaceutical companies. The most seldom used sources of information for prescribing decisions in pain clinics were systematic reviews produced by The Cochrane Collaboration. The previous nation-wide study showed that Croatian physicians lack knowledge about evidence-based medicine (EBM) and are not familiar with Cochrane systematic reviews (34). Activities of the Cochrane Croatia, which was founded in 2009, have focused on building awareness about EBM and systematic reviews in Croatia and neighboring countries (35). A study conducted among medical students has shown that those exposed to EBM curriculum have better knowledge and more positive attitudes towards EBM (36). It

is expected that further educational activities of the Cochrane Croatia may contribute to increased awareness of physicians about evidence in medicine.

Most of the contacts with pharmaceutical companies in pain clinics in Croatia involved visits by pharmaceutical company representatives, obtaining funding for attending scientific meetings and CME courses. It has been shown that contact with pharmaceutical companies should be limited in order to obtain prescribing treatment based on scientific evidence (37). In the Croatian Health Care system, pharmaceutical companies frequently send their representatives to meet with physicians (38). There is a Contract from 2010 on ethical marketing aimed towards regulating contacts between representatives of pharmaceutical companies and physicians, but it is not known what the effects of this Contract are (39).

In this study, few physicians and other employees of pain clinics had scientific and academic titles or a research project, and data collected in pain clinics were rarely used for research purposes. The research results gained in everyday practice can be immediately applied to patients and are necessary for the implementation of EBM (40). Earlier analysis of bibliometric trends on research in the field of pain in Croatia has shown an upward trend in research on pain, but these research activities were modest and of low quality (41). Therefore, it would be advisable to strengthen the Croatian research capacity in the area of pain for the benefit of patients.

A limitation of this study is its cross-sectional design. Collecting additional information about pain clinics would provide even more information about their organization and services. Further studies on this subject could explore in more detail the number of different drugs and therapies prescribed in the pain clinics, advanced interventions, type of training for pain clinic staff, possibility to train on cadavers and number of workshops organized by pharmaceutical and other companies attended by the pain clinic staff.

Conclusion

The national study about tertiary outpatient pain clinics in Croatia showed that they suffer from a number of weaknesses. Since pain is a major public health issue, pain clinic staff should engage more in research to contribute to the growing field of pain research, to enhance capacities for pain research in Croatia, to incorporate scientific evidence into their daily decision-making and to enable evidence-based practice.

What is already known on this topic

- *The first pain clinic was established in 1961 in the USA.*
- *Pain clinics are an important part of health care specialized for pain management.*
- *It is advisable to have professionals from different health-related disciplines in pain clinics for the treatment of complex pain disorders.*

What this study adds

- *This is the first national survey of pain clinics in Croatia.*
- *Most of the pain clinics in Croatia have been founded in the last 15 years and their geographic distribution leans towards central Croatia.*
- *Pain clinics in Croatia mostly employ only physicians and nurses.*
- *Many treatments available in the analyzed pain clinics are not evidence-based.*
- *Pain clinic employees have frequent contacts with pharmaceutical industry representatives.*
- *Research activities in the analyzed pain clinics are scarce.*

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

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Appendix 1. Questionnaire

Dear Sir/Madam,
This study is conducted in agreement with the Croatian association for the treatment of pain (HDLB). The aim of the questionnaire is to gain insight into organization and practice of pain clinics in Croatia. Overview of the conditions and practices of pain clinics in Croatia will enable us to provide recommendations for improvement and to coordinate activities on a national level, with the goal of improving pain management.
The questionnaire is intended for the heads of the pain clinics. We would kindly ask for very precise responses. We thank you in advance for participating in this study.

General information about the pain clinic

- Hospital where the pain clinic is located? _____
- Head of the pain clinic: _____
- Contact of the pain clinic head: _____
- When was the pain clinic founded (year)?_____
- What is the surface area of the space where pain clinic is located? _____
- How many physicians are employed in pain clinic and what are their specialties? _____
  _____
- How many nurses are employed in the pain clinic?_____
- How many professionals work in the pain clinic, which are not physicians or nurses?
  _____
- Please indicate background of those other professionals _____
  _____
- Do you have contract with Croatian Health Insurance Fund? Yes No
- Do you write patient records with a printer? Yes No
- Dou you have archives of treated patients' records? Yes No
- If yes, do you have electronic archives? Yes No
- Is the pain clinic open every working day? Yes No
- How many hours per week is the pain clinic open to patients? _____ h
- How many patients, on average, visit the pain clinic per week? _____
- How many first visits, on average, do you have per week? _____
- Are the data for the previous two questions based on the regular statistical follow-up of the pain clinic activities? Yes No
- If the pain clinic has electronic archives of patients' records, can these archives be used to retrieve data about therapies and diagnoses? Yes No
- Please indicate the 5 most common diagnoses in the pain clinic _____
  _____

Therapeutic procedures
- What type of therapeutic procedures the pain clinic offers (multiple answers allowed):
  a) Pharmacotherapy
  b) Regional blocks
  c) Trigger point injections
  d) Epidural analgesia

e) Epidural catheter
f) Intrathecal administration of drugs
g) Subcutaneous administration of drugs
h) TENS
i) Magnetic therapy
j) Ultrasound
k) Laser therapy
l) Acupuncture
m) Other _____

- Does the pain clinic offer complementary medicine therapies? Yes No
- If yes, please indicate which ones: _____
  _____
- Does the pain clinic offer alternative medicine therapies? Yes No
- If yes, please indicate which ones: _____
  _____

Professional activities
- Do the pain clinic employees organize continuing medical education courses?
  Yes No
- Do the pain clinic employees organize educational activities for lay persons and patients?
  Yes No
- Does the pain clinic offer educational materials for patients? Yes No
- Does the pain clinic offer educational materials for patients that were prepared by the pain clinic employees? Yes No
- Does the pain clinic offer educational materials for patients that were prepared by the HDLB or another professional organization? Yes No
- Does the pain clinic offer educational materials for patients that were prepared by the pharmaceutical companies? Yes No

How do you choose which drugs will you prescribe (multiple answers allowed):
a) Based on information from research symposia
b) Based on research articles
c) Based on The Cochrane Library
d) Based on materials provided by pharmaceutical companies
e) Based on consultations with colleagues

Relations with pharmaceutical companies

- Do the pain clinic employees have a contact with pharmaceutical industry representatives?
  Yes No
- How many physicians from the pain clinic were sponsored by pharmaceutical industry in any way during the last year? _____
- Please describe type of contact with pharmaceutical industry representatives:
  a) Conversation with drug reps and receiving promotional materials about their products
  b) Financing research symposia organized by the pain clinic employees

c) Financing organization of continuing medication courses
d) Financing travel expenses and fees for attending research conferences
e) Financing travel expenses and fees for continuing medical education
f) Representation (dinners, socializing with pharmaceutical companies' representatives)
g) Donations for buying equipment used for treatment and diagnostic purposes
h) Donations for buying equipment that is not used for treatment and diagnostic purposes

What was the total cost of all pharmaceutical companies' investment during the last year for all those activities indicated above, in the pain clinic (expenses of all activities combined):

a) less than 10.000 HRK
b) 10.000 – 30.000 HRK
c) 30.001 – 70.000 HRK
d) more than 70.000 HRK

Research profile

- How many physicians employed in the pain clinic have a MSc degree? _____
- How many physicians employed in the pain clinic have a PhD degree? _____
- How many physicians employed in the pain clinic have an academic title (assistant, associate or full professor)? _____
- How many other pain clinic employees have an academic title (assistant, associate or full professor)? _____
- How many pain clinic employees have a research project? _____
- Who is financing the research project(s) and what is its value? _____
- Do you use data collected in the pain clinic for research purposes? Yes No
- How many research publications did pain clinic employees published in the last 5 years that are indexed in CC and in Index Medicus:
  a) CC: _____
  b) Index Medicus: _____
- How many of those research publications are studies from the field of pain and published in the pain-related journals?
  a) CC: _____
  b) Index Medicus: _____

Original article

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Morphological and morphometric analysis of the shape, position, number and size of mental foramen on human mandibles

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Objective. To provide anatomical information on the position, morphological variations and incidence of mental foramen (MF) and accessory mental foramen (AMF) as they are important for dental surgeons, anesthetists in nerve block and surgical procedures, to avoid injury to the neurovascular bundle in the mental foramen area. **Methods.** Our study was conducted on 150 adult dry human mandibles from the osteological collection of the Department of Anatomy of the Faculty of Medicine, University of Sarajevo. The location and shape of the MF and the presence of the AMF were studied by visual examination. The size and position of the MF were measured using a digital vernier caliper. SPSS, version 17 software was used for the statistical analysis. **Results.** Bilateral mental foramina were presented in all 150 mandibles. In the majority of mandibles, the MF was located between the first and second premolar (20.3%) or on the level of the root of the second premolar (60.3%), midway between the inferior margin and the alveolar margin of the mandible. Most of the mental foramina were oval in shape (83.3%). An AMF was present in four mandibles (2.7%) on the right side. **Conclusion.** This study may be a very useful new supplement to data on variations in the incidence, position, shape and size of mental and accessory mental foramina, which may help surgeons, anaesthetists, neurosurgeons and dentists in carrying out surgical procedures successfully.

Introduction

The mental foramen (MF) is a small foramen situated in the anterolateral aspect of the body of the mandible. Normally, the MF is located below the interval between the premolars. It transmits the mental nerve, an artery and a vein. The mental nerve is a branch of the inferior alveolar nerve which supplies sensation to the lower lip and the labial mucosa and lower canines and premolars. Variations in the position of the MF have been reported by many authors in different ethnic groups (1, 2) and various shapes have also been noticed (3). Any foramen in addition to the MF in the body of the mandible is known as an accessory mental foramen (AMF). The AMF transmits the accessory branch of the mental nerve.

Precise knowledge on variations in the position, shape, and the size of the MF and the presence of the AMF would be of great use for dental surgeons while performing surgical procedures on the mandible, such as curet-

tage of premolars, filling procedures, dental implants, root canal treatments, orthognatic surgeries, etc. It is also essential to have effective and a successful anesthesia during nerve blocks, prior to surgical procedures (4).

Many studies have been reported by various authors, which were carried out on different ethnic groups and on populations of different races, but such studies reported in the Bosnian population are sparse. Hence, an attempt was made in our present study to determine the most common position and size of the MF in adult Bosnian mandibles, which may be useful for future implications in our Bosnian population.

Methods

The mandibles used for our study were procured from the Department of Anatomy, Faculty of Medicine, University of Sarajevo. 150 adult dry mandibles, irrespective of age and sex, with either all the teeth intact or with preserved alveolar margins, were used for our study. The number, shape and the positions of the MF were determined by a visual examination. The positions of the MFs were measured with respect to the teeth, for which we followed the Tebo and Telford classification (5): I=The MF is projected between the canine and first premolar; II=The MF is projected at the level of the first premolar; III=The MF is projected between the first and second premolars; IV=The MF is projected at the level of the second premolar; V=The MF is located in between the second premolar and first molar; VI=The MF is located at the level of the first molar (Figure 1).

Morphometric analysis

We measured the distance of the MF (in mm) from various landmarks, including the

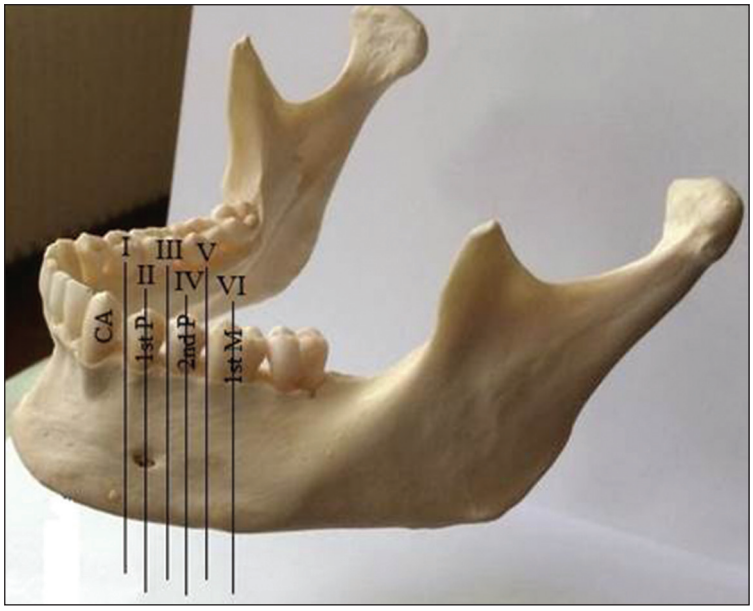

Figure 1 Location of the mental foramen compared to the teeth (I-VI): CA=canine; 1stP=first premolar; 2ndP=second premolar; 1stM=the first molar; I=The MF is projected between the canine and first premolar; II=The MF is projected at the level of the first premolar; III=The MF is projected between the first and second premolars; IV=The MF is projected at the level of the second premolar; V=The MF is located in between the second premolar and first molar; VI=The MF is located at the level of the first molar.

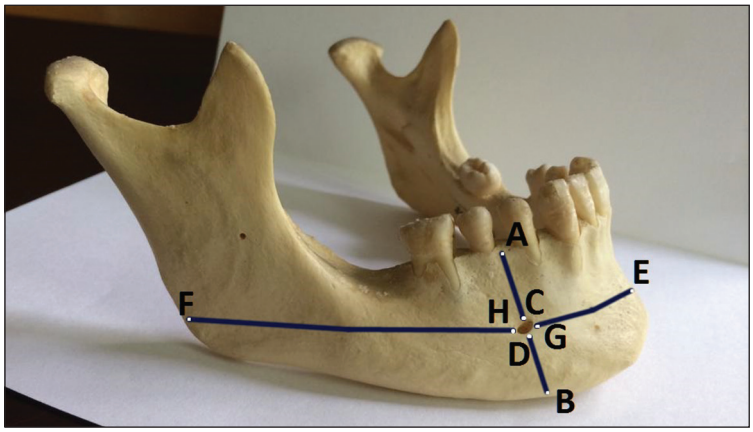

Figure 2 Position of the MF and its size calculated by transverse and vertical measurements of the mandible in relation to borders AB: The distance from the bottom edge of the mandible body to the processus alveolaris; AC: The distance from the processus alveolaris to the upper edge of the foramen mental; BD: The distance from the bottom edge of the mandible body to the bottom edge of the MF; CD: The height or vertical diameter of the MF [AB–(AC+BD)]; EF: The distance from the mental symphisis to the back edge of the ramus mandibulae; EG: The distance from the mental symphisis to the front edge of the MF; FH: The distance from the back edge of the ramus mandibulae to the back edge of the MF; GH: The horizontal width or diameter of the MF [EF–(EG+FH)].

symphysis menti, the alveolar crest, the posterior border of the ramus of the mandible, and the lower border of mandible, with digital vernier calipers, and calculated the size of the MF. The measurement of all parameters was performed on both sides (Figure 2).

Statistical analysis

Data were analyzed using SPSS version 17. The location and size of the MF were determined by the minimum and maximum values, mean and standard deviation. Testing differences in the position and dimensions of the MF between men and women was performed using the Mann-Whitney test. The chi-square method was used to examine the difference in the location of the MF compared to the teeth on the left and right sides. We also analyzed differences in those parameters between males and females. All statistical results where $p<0.05$ were considered statistically significant.

Results

The Mental foramen

In our present study, 150 bones (100%) showed a single MF on the left side and 147 (97.3%) showed a single foramen on the right side. The most common position of the MF on the examined mandibles on the right side was on the longitudinal axis of the second premolar (position IV), followed by positions III, II, V. No MF was observed in positions I and VI in any mandible. The most common position of the MF on the examined mandibles on the left side was on the longitudinal axis between the first and second premolars (position III), followed by positions IV, II, V and VI. No MF was observed in position I in any mandible. A statistically significant difference was found in the location of the MF compared to the teeth on the right and left sides using chi-square test $p<0.05$.

Table 1 The difference in mental foramen (MF) location compared to the teeth and interalveolar septum on the right side between the genders

Gender	Position (right side)						
	I	II	III	IV	V	VI	Total
Male	-	4	21	63	9	0	97
Female	-	2	9	29	13	0	53
Total	-	6	30	92	22	0	150

I=The MF is projected between the canine and first premolar; II=The MF is projected at the level of the first premolar; III=The MF is projected between the first and second premolars; IV=The MF is projected at the level of the second premolar; V=The MF is located in between the second premolar and first molar; VI=The MF is located at the level of the first molar.

Table 2 The difference in mental foramen (MF) location compared to the teeth and interalveolar septum on the left side between the genders

Gender	Position (left side)						
	I	II	III	IV	V	VI	Total
Male	-	2	24	59	9	3	97
Female	0	2	7	30	14	0	53
Total	0	4	31	89	23	3	150

I=The MF is projected between the canine and first premolar; II=The MF is projected at the level of the first premolar; III=The MF is projected between the first and second premolars; IV=The MF is projected at the level of the second premolar; V=The MF is located in between the second premolar and first molar; VI=The MF is located at the level of the first molar.

The chi-square test showed that there was no statistically significant difference in MF location regarding the left or right sides, when comparing teeth between men and women. On the right side: p=0.994, and on the left: p=0.810. These results are presented in Tables 1 and 2.

With respect to the superior and the inferior borders of the mandible, most of the MF were found to occupy the mid position.

The MF was positioned at an average distance of 14.37±4.22 mm from the alveolar margin on the left side, whereas it was positioned at a distance of 14.37±4.37 mm on the right side. From the symphysis menti, the MF was located at a distance of about 25.65±2.11 mm on the left side and at a distance of about 25.61±1.93 mm on the right side. The average distance of the MF from the posterior border of the mandible was 58.68±4.70 mm on the left side and 59.34±4.50 mm on the right side. From the base of the mandible, it was located at a distance of 12.72±1.66 mm on the left side and at a distance of 12.67±2.00 mm on the right side. The mean vertical diameter of the MF in our study was 1.71 mm±1.02 mm on the right side and 1.69 mm±0.64 mm on the left side, respectively, and the mean horizontal diameter was 2.56 mm±1.05 mm on the right side and 2.41 mm±0.94 mm on the left side (Table 3).

Shape

In 150 bones, (83.3%) the MF bilaterally showed an oval shape and in the remaining 25 mandibles (16.7%) the MF bilaterally showed a round shape.

The Accessory mental foramen

Among the researched material there were 4 cases, or 2.7%, in which the existence of an AMF was reported, and its location in all four cases was on the right side (Figure 3).

Table 3 Morphometric measurement values

Morphometric measurement	Side	$\bar{x} \pm SD$	Range
The distance from the bottom edge of the mandible body to the processus alveolaris	Right	28.79 (5.167)	13-44
	Left	28.79 (4.979)	16-42
The distance from the processus alveolaris to the upper edge of the foramen mental	Right	14.37 (4.371)	1-24
	Left	14.37 (4.223)	2-25
The distance from the bottom edge of the mandible body to the bottom edge of the MF	Right	12.67 (2.008)	2-19
	Left	12.72 (1.665)	8-16
The height or vertical diameter of the MF [AB– (AC + BD)]	Right	1.71 (1.027)	1-11
	Left	1.69 (0.645)	1-4
The distance from the mental symphisis to the back edge of the ramus mandibulae	Right	87.52 (4.861)	71-102
	Left	86.75 (4.872)	75-101
The distance from the mental symphisis to the front edge of the MF	Right	25.61 (1.931)	21-32
	Left	25.65 (2.115)	20-32
The distance from the back edge of the ramus mandibulae to the back edge of the MF	Right	59.34 (4.506)	46-71
	Left	58.68 (4.701)	43-71
The horizontal width or diameter of the MF [EF – (EG + FH)]	Right	2.56 (1.052)	1-7
	Left	2.41 (0.943)	1-5

MF=Mental foramen; AB=The distance from the bottom edge of the mandible body to the processus alveolaris; AC=The distance from the processus alveolaris to the upper edge of the foramen mental; BD=The distance from the bottom edge of the mandible body to the bottom edge of the MF; EF=The distance from the mental symphisis to the back edge of the ramus mandibulae; EG=The distance from the mental symphisis to the front edge of the MF; FH=The distance from the back edge of the ramus mandibulae to the back edge of the MF.

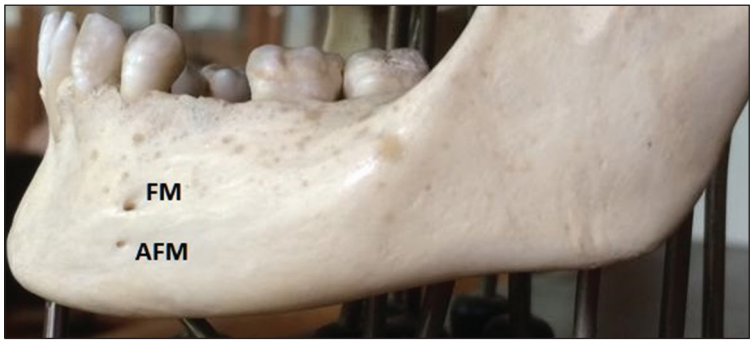

Figure 3 Typical location of the mental foramen in the area of the second premolar; Below the mental foramen an accessory mental foramen is noted.

Discussion

The location of the MF is an important factor when considering the mental incisive anesthetic block and surgery in the outer premolar mandibular region (6). There are significant differences reported in the location of the MF among different ethnic groups (7). Igbigbi and Lebona (8) in Malawians and Mbajiorgu (9) in Zimbabweans mandibles reported position IV as the most common followed by position V. However, Santini and Land (10) in British and Green (11) in Chinese mandibles observed position III as the most common, followed by position IV. In other studies on Kenyan mandibles (12), position III was found to be most common, followed by position II, and

in the Malay populations (13) the most common position was IV, followed by III, but in these studies the right and left sides were not considered separate from each other. In the present study, we considered right and left sides separately.

The most common position of the MF on the right side was on the longitudinal axis of the second premolar (position IV) and on the left side it was on the longitudinal axis between the first and second premolars (position III). Our results are similar to the results presented in their studies by other authors (14-16), who also did a separate analysis of the right and left sides. Variability in MF position may be related to different feeding habits, subsequently affecting mandibular development (16). Prior knowledge of common positions in local populations may be helpful in effective nerve blocks and surgeries in those regions.

Knowledge of the average distance between the MF and the medial line and mental symphisis is important in clinical practice, because this foramen cannot be palpated or visualized, but its location is determined using the teeth (17). However, in cases of toothless mandibles, these values are used to locate the MF. In addition, other parameters may be used, such as the average distance between the foramen's lower edge on the mandible and the alveolar process or the angle of the mandible (17). All morphometric measurements in this paper are presented in the "Results" section and are similar to the results of previously conducted studies, but also within these studies racial and gender differences are registered. Many of the differences may be attributed to the nutrition habits of the population which affect the development of the mandible and the entire digestive system (10, 16, 18).

We also measured the size of the MF. The mean vertical diameter (CD) of the MF in our study was 1.71 mm ± 1.02 mm on the right side and 1.69 mm ± 0.64 mm on the left side, respectively, and the mean horizontal diameter (GH) was 2.56 mm±1.05 mm on the right side and 2.41 mm±0.94 mm on the left side, respectively. These results are very close to those of Igbigbi and Lebona (8). However, Oguz and Bozkir (19) did measurements in 34 dry mandibles of people from Turkey and found 3.14 mm on the left side, and a mean vertical diameter of 2.38 mm and 2.64 mm on the right and left sides, respectively. The present results differ significantly for HD from those of Oguz and Bozkir (19). In another study conducted by Singh and Srivastav (20), only the horizontal diameter was taken and the results showed the mean horizontal diameter to be 2.79 mm on the right side and 2.57 mm on the left side, again much less than in the present study. The probable reason for the significant difference in HD in their study was the higher number of round than oval MF.

In the present study, we observed an oval-shaped MF in 83.3% mandibles and a round-shaped MF in 16.7%. The domination of the oval shape compared to the round shape was noted by other authors as well (21-23). The incidence of AMF varies in the literature. Singh and Srivastav (20) observed AMF in 13% mandibles. Gershenson et al. (24) examined 525 dry mandibles and reported that 4.3% mandibles had a double MF and 0.7% mandibles had triple MF. However, Serman (25) reported the incidence of AMF to be 2.7%. In the present study, we observed an AMF in 4/150 (2.7%). An AMF is due to the branching of the mental nerve prior to its passing through the MF. Thus, the verification of the existence of an AMF would prevent nerve injury during periapical surgery.

Conclusion

Paralysis of the mental nerve is one of the principal complications of surgery of the mandibular canal and MF regions. There-

fore, identification of the MF in its various positions and its morphometric analysis is important for dental surgeons in nerve block and surgical procedures, such as apical curettage of mandibular premolars and periodontal surgery, to avoid injury to the neurovascular bundle. In the majority of mandibles, we found an oval shaped foramina lying in position IV. However, variations exist in the position, shape, and size of the MF in different population groups. It is essential to be aware of the possibility of these anatomical variations while planning surgery in that region, to avoid nerve damage and also to enable effective mental nerve block anesthesia.

What is already known on this topic

- *The position of the mental foramen has been reported to vary in different ethnic groups and in different historical populations.*
- *The location of the mental foramen is used in a number of maxillofacial surgical procedures and in anthropological examinations.*

What this study adds

- *This study has shown that this is the most common shape, position, number and size of MF in adult Bosnian mandibles, which may be useful and have future implications in our Bosnian population.*
- *The results of this research related to the position and direction of the mental foramen are similar to the results of research undertaken on the European population published so far.*

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

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

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Original professional article

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Tumor marker CA 15-3 in breast cancer patients

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Objective. The aim of this study was to determine whether there is a correlation between the serum concentration of the tumor marker CA 15-3 and breast cancer, which has not been proven by the existence of regional and distant metastases, and breast cancer with the presence of regional and distant metastases. **Patients and methods.** The study was a retrospective-prospective study, and was conducted on 100 women aged 40-70 years of age in the period of January 2007 until June 2011, in whom, after surgery, breast cancer was histologically verified, where before the surgery serum tumor marker CA 15-3 levels were established. The serum tumor marker CA 15-3 concentrations are determined in all patients after radiological diagnosis of suspected breast cancer (radiological findings concluded as BI RADS 4 and 5). The study excluded patients with liver cirrhosis, liver cancer and lung cancer. The study group consisted of patients with metastatic breast cancer, and the control group of patients with breast cancer comprised those shown to be without verified metastatic disease. To calculate the correlation, Spearman's correlation coefficient was used. A difference in p values of less than 0.05 ($p<0.05$) was considered statistically significant. **Results.** The serum tumor marker CA 15-3 was elevated in all patients with proven remote or clubbing metastasis in 35.5% of patients with metastasis spreading to regional lymph nodes. **Conclusion.** There is a significant correlation between serum concentrations of the tumor marker CA 15-3 and the presence of metastasis, and serum concentrations of tumor markers and the dissemination of the underlying disease.

Introduction

Breast cancer is stage-biological process causing multiple genetic and epigenetic changes in the epithelial cells of the breast over a period of several years (1). The biological progression of breast cancer is based on the inability of differentiation, loss of contact inhibition, uncontrolled growth, the ability to migrate, invasion, angiogenesis, metastasis, and the ability to avoid immune control of tumor cells. Breast cancer tumor cells generally retain the morphological and functional characteristics of normal tissue cells. They possess special molecules that have arisen in the course of malignant transformation. Many of these new tumor cell molecules are immunogenic, i.e. they are able to induce a humoral and / or cellular immune response. These reactions occur in patients with cancer, or in animals immunized with breast cancer cells. These specific antigens are classified into two groups: tumorospecific (TSA) and tumoroassociated (associated) antigens (TAA) (1).

Circulating tumor antigens and markers are shown in the serum. For this purpose only the monoclonal antibodies-TAA: CEA and CA 15-3 are used. CEA (carcinoembryonic antigen) is a heterogeneous glycoprotein, with a molecular weight of 150 to 300 kDa, whose serum concentrations are abnormally elevated in patients with colorectal cancer, breast cancer and other cancers (2, 3). The values may be increased in heavy smokers and nonmalignant diseases (4). CA 15-3 is a glycoprotein with a molecular weight of 300-450 kDa. It is elevated in breast, ovarian, pancreatic, lung and colorectal cancers (5).

The European Group on Tumor Markers (EGTM) recommended determining serum levels of tumor markers during the follow-up of treated breast cancer patients (6). EGTM defines a significant increase in concentration of tumor markers if its value is increased at least 25% compared to the reference value.

The frequency and level of each tumor marker in the serum depends on the clinical extent of the disease. The frequency of positive findings was significantly higher in patients with metastatic compared to clinically confined disease. A comparative study of CEA and CA 15-3 shows that CA 15-3 is a more sensitive marker than CEA. The frequency of both markers was greatest in patients with metastatic lesions in the liver. Increased levels of the markers CEA and CA 15-3 can be detected on average 3-8 months before a definitive clinical diagnosis of metastases (1). Tests for determination of tumor antigens in serum have been proven to be a useful tool for monitoring treatment response in breast cancer patients (5).

The aim of this study was to determine whether there is a correlation between the serum concentration of the tumor marker CA 15-3 and primary breast cancer, where the existence of regional and distant metastases has not been shown, and breast cancer with the presence of regional and distant metastases, and thereby indicate the diagnostic value (or lack of value) of the tumor marker CA 15-3 in the detection of primary breast cancer.

Patients and methods

The study was a retrospective-prospective study, and was conducted on 100 women aged 40-70 years of age in the period from January 2007 to June 2011, in whom after surgery breast cancer was histologically verified, and for whom before the surgery serum tumor marker CA 15-3 concentrations were established. The study excluded patients with liver cirrhosis, liver cancer and lung cancer. Studies for serum tumor markers CA 15-3 were performed in those patients in whom ultrasound and mammography showed suspected breast cancer (radiological findings BI RADS 4 and 5). Patients were divided into two groups in relation to the presence of metastases: the study and the control group. The study group consisted of 50 patients in whom breast cancer had been histologically verified and in whom after surgical removal of the content of the axillary lymph nodes the existence was shown histologically of metastases in the regional lymph nodes, and other available diagnostic methods had proved the presence of distant metastases. Given the localization of secondary deposits, patients from the study group were divided into two subgroups: firstly the subgroup of patients in whom breast cancer was proven with metastases to regional lymph nodes by histopathological analysis of tissue samples, and secondly the subgroup patients in whom, alongside the presence of cancer in the breast and metastases to the regional lymph nodes, the presence of distant and associated metastases had been shown.

The control group consisted of 50 patients in whom breast cancer had been histologically verified, and in whom, after surgical removal of the contents of the axillary

lymph nodes, the existence of metastases in the regional lymph nodes had been excluded by histopathology, and other available diagnostic methods had excluded the existence of distant metastases. Mammography and breast ultrasound examinations were performed at the Department of Radiology and Nuclear Medicine, Clinical Center, Tuzla. Mammography was performed using a digital mammography machine, Simens brand-Mammomat 3000 NOVA with cassette sizes 18x24 and 24x30 cm. Standard mammographic projections were made: craniocaudal and mediolateral.

Ultrasound examinations of the breasts were performed using the ultrasound machine "sonoline G60S" Siemens, with linear probes measuring 7.5 and 12 MHz. Mammography and breast ultrasound findings were interpreted by two radiologists and classified by BI RADS classification into one of five categories: 1. Breasts where no pathological lesions are seen; 2. Benign findings; 3. Probably benign findings; 4. Lesions suspicious for malignancy; 5. Lesions highly suspicious for malignancy-malignant lesion.

In patients with changes in the breasts, whose ultrasound and mammography findings were classified as BI RADS 4 or BI RADS 5, serum tumor marker CA 15-3 concentrations were taken by sequential Chemiluminiscence Immulite 2000 BR-MA system analysis and quantitative measurement of serum levels of CA 15-3 antigens in human serum on ABBOT apparatus. The reference values of serum concentrations of tumor markers CA 15-3 were 0 to 31.3 U/ml. Significantly elevated values were considered to be values 25% greater than the upper reference value, or greater than 39.25 U/ml.

Statistical analysis

For statistical analysis, we applied standard methods of descriptive statistics, such as: relative numbers (%), measures of central tendency, measures of variability, parametric z and t-test, and test of proportions. To test the statistical significance of differences between respondents we used the Student t test. To calculate the correlation we used Spearman's correlation coefficient. The difference between the samples was considered significant when p was less than 0.05 ($p<0.05$).

Results

The study included 100 patients with histologically verified breast cancer, with an average age of 55.27±8.16 years. The average age of the patients in the study group was 54.74±8.41 years, while the control group was 55.8±7.94 years old. There was no significant difference in age between the patients in the study and the control group ($p>0.05$). Preoperative ultrasound and mammography findings in 28% patients were concluded as BI RADS 4, and in 72% patients as BI RADS 5. In the control group of patients there were 50 patients with breast cancer detected by histopathologic analysis of tissue samples, and histopathological evaluation of the content of the axillary metastatic axillary lymph nodes had excluded the existence of metastases. In this group of patients the serum tumor marker CA 15-3 was within the reference values from 2.7 to 26.7 U/ml.

All patients from the study group, 50 of them (100%), had proven metastases in the regional lymph nodes, and 19 of them (38%), alongside the proven metastases in the regional lymph nodes, also had distant metastases. In this group of patients significantly elevated levels of serum tumor marker CA 15-3 were also shown, with a mean value of 214.70 U/ml. Taking into account the localization of the metastatic processes, the statistically highest serum concentrations of the tumor marker CA 15-3 were detected in patients with metastasis in the bones, as well as in patients in whom metastatic processes were demonstrated in several organs or organ systems.

In the group of patients with metastasis only in the regional lymph nodes, serum tumor marker CA 15-3 levels ranged from 11.2 U/ml and 61.3 U/ml. There was no statistically significant correlation between serum levels of tumor markers CA 15-3 and the number of axillary lymph nodes affected.

Taking into account the concentrations of the serum tumor marker CA 15-3 in the study group in 40% of them were within the reference values, in 10% of them were elevated, and in 50% of them they were significantly elevated. In the control group of patients, values of serum tumor marker CA 15-3 were within the reference values.

Student's t-test showed that concentrations of the serum tumor marker CA 15-3 were statistically significantly higher in the study group than in the control group ($p<0.0001$). The same test showed that the concentrations of the serum tumor marker CA 15-3 were significantly lower in the study group than the threshold, indicating increased concentrations ($t=21.0$; $p<0.0001$), whereas serum tumor marker CA 15-3 concentrations in the study group were significantly higher than the value that indicates significantly elevated concentrations of tumor markers CA 15-3 ($t=3.2$; $p=0.001$). Student's t-test showed that serum tumor marker CA 15-3 concentrations in the study group were significantly higher in the subgroup of patients with the presence of distant metastasis ($p<0.0001$) than in the subgroup of patients with metastases in the regional lymph nodes only.

The most common location of metastasis were the bones (52.6%), followed in frequency by associated metastases, where secondary deposits could be found in two or more organs or organ systems (31.6%). The incidence of associated metastases did not differ significantly statistically, as evidenced by the test of proportions ($z=1.31$; $p=0.189$). Bone metastases were significantly more likely than those in other organs: the liver, CNS and lungs ($Z=3.2$; $p=0.0013$). The same conclusion was reached by comparing the incidence of associated metastases and metastases in the CNS, liver and lungs ($Z=2.9$; $p=0.036$) (Figure 1).

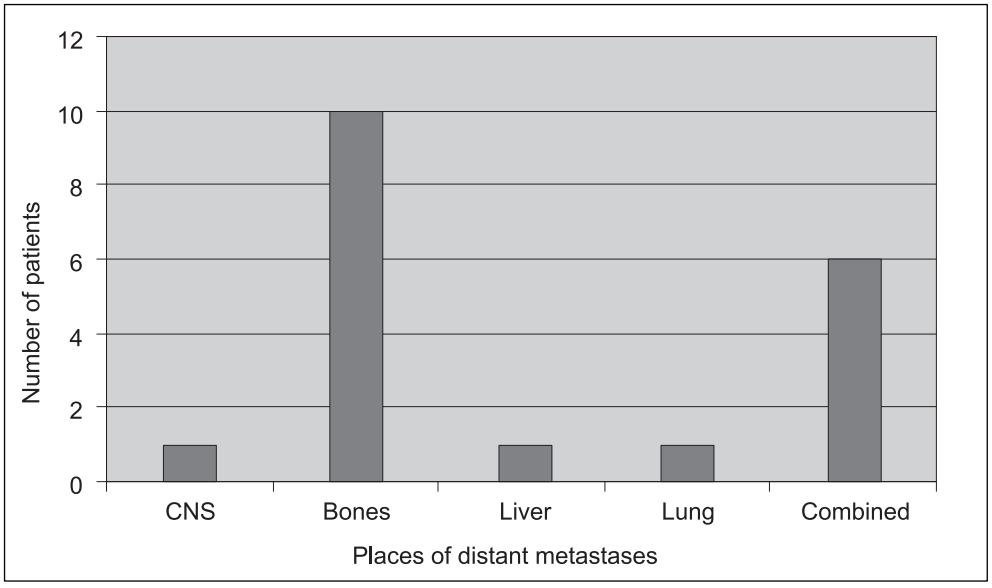

Figure 1. Distribution of patients with respect to the localization of distant metastases.

Student's t-test showed that the concentrations of serum tumor marker CA 15-3 were statistically significantly higher in patients with associated distant metastases than in patients in whom metastases were present in the axillary lymph nodes only ($t=4.5$; $p=0.001$).

A statistically significant positive correlation was found between serum levels of tumor markers CA 15-3 and the presence of distant metastases ($\rho=0.83$; $p<0.0001$).

Discussion

Numerous studies have confirmed that CA 15-3 and BR 27.29 are the best serum tumor markers of breast cancer available. The use of the currently available serum tumor markers is limited by their low sensitivity and specificity for early diagnosis. Consequently, the available markers are of no value in either screening or diagnosing early breast cancer (7).

However, serial measurement of these markers can result in the early detection of the recurrent disease, as well as indicating the efficacy of therapy (8). Other markers, mainly epitopes present on mucin glycoproteins (CA549, CA M26, CA M29, CA27.29) are under evaluation, but to date none have been shown to be more useful than CA 15-3. These other markers may be used instead of CA 15-3, but not in combination (9).

The sensitivity of tumor markers in the diagnosis of local recurrence is poor, but their usefulness (particularly that of CA 15-3) in the early diagnosis of breast cancer metastases is clear. The early detection of metastatic disease does not benefit the patient in terms of overall survival or time to the appearance of clinical signs (9).

Therefore, tumor markers are not recommended for any group of patients for screening, diagnosis, or monitoring of patients with breast cancer. Although high serum tumor marker CA 15-3 levels usually indicate an extended illness, not enough data are available to allow inclusion of tumor markers in routine monitoring of breast cancer. Both tumor marker CA 15-3 and BR 27.29 have "Food and Drug Administration" approval for monitoring patients suffering from breast cancer with advanced disease, but such authorization does not necessarily mean clinical value. The main obstacles in relation to the use of tumor markers CA 15-3 as indicators of asymptomatic recurrences include the low incidence of elevated serum concentrations of tumor marker CA 15-3 in the early stages of the disease. Although the use of tumor markers CA 15-3 and BR 27.29 is not recommended in routine work and monitoring of breast cancer, but only for monitoring response to treatment, the guidelines of the American Society of Clinical Oncology (ASCO) support the use of these markers, since these tumor markers can indicate the progression of the disease, while all other measurable parameters are important in monitoring breast cancer using reference value ranges (10).

The National Academy of Clinical Biochemistry (NACB), EGTM, and SOR (the standards, options and recommendations offshore project in 1993, France) recommend that serum tumor markers CA 15-3 and BR 27.29 should be used with care, as an aid in monitoring the clinical disease in patients suffering from breast cancer. EGTM and SOR guidelines also recommend the use of serum concentrations of tumor markers CEA in patients with breast cancer.

The study by Vrdoljak et al. (11) which included 177 patients, investigated the relationship between serum levels of tumor marker CA 15-3 and metastases to regional lymph nodes in patients with breast cancer. In this study, 73% of patients with histologically verified metastases in regional lymph nodes had normal serum tumor markers CA 15-3, while 27% had elevated serum concentrations of tumor marker CA 15-3. In

most studies conducted worldwide it is indicated that the value of tumor marker CA 15-3 is elevated in the group of patients with advanced disease. The study by Berberoglu et al. (12), which was conducted on a cohort of 60 patients, in 68% of patients with positive lymph node metastasis in the axillary lymph nodes, elevated serum tumor marker CA 15-3 was present, while in the group of patients with distant metastases increased levels of serum tumor marker CA 15-3 were present in all patients (100%).

According to the data, Berberogluoa et al. (12) serum tumor marker CA 15-3 had a mean value of 39.1 in the group of patients with proven metastases in the axillary lymph nodes, with deviation of 1.2 U/ml. A study by the same authors concluded that the tumor marker CA 15-3 is the tumor-specific marker in the diagnosis and especially the monitoring of breast cancer patients. The same authors suggest that elevated levels of the tumor marker CA 15-3 can be detected in 1% of the healthy population, 3%-20% of benign changes in the breast, 36%-40% of hepatitis and 14%-70% of cancer of the gastrointestinal tract and lungs.

The study by Laesing et al. (13), conducted in 2007 on a group of 119 patients with proven breast cancer and regional and distant metastases present, made a correlation between serum concentrations of tumor markers CA 15-3 and the localization of the metastases. Eighty patients (67.2%) had metastases present only in one place, in the liver (19.3%) or the bones (21.9%). 39 patients had metastasis in multiple organs or organ systems. Patients with metastasis to the bones and liver had elevated serum tumor marker CA 15-3: with a median of 110 U/ml and 81 U/ml, compared to patients with metastasis to the lungs and lymph nodes: median 48.4 U / ml and 20.2 U/ml. As for the correlation between the serum concentrations of tumor marker CA 15-3 and localization of metastases, the results are often conflicting: research by Berruti et al. (14) showed that the prevalence of elevated serum levels of tumor markers CA 15-3 varies depending on the localization of the metastases. Patients with involvement of visceral organs had elevated serum tumor markers CA 15-3 more often than patients with involvement of bones and soft tissue. The highest sensitivity, in terms of elevated serum concentrations of tumor markers CAE and CA 15-3, was found in patients with pleural effusion.

Al-Jarallah et al. (15) reported that the median serum levels of CA 15-3 or CEA tend to increase depending on the localization of the metastases. The highest serum concentrations of the tumor marker CA 15-3 were found in patients with bone metastases, while the highest serum concentrations of tumor marker CEA were found in patients with metastasis to the lungs, bones or liver. Serum tumor marker CA 15-3 was elevated in more than 90% of patients with advanced disease and metastasis to the lungs, bones or liver.

Studies by other authors have agreed that the tumor marker CA 15-3 is mainly more sensitive in the presence of bone and visceral metastases. Similar results were obtained in the study by Laessing et al. (13), where they demonstrated elevated serum levels of the tumor markers CA 15-3 and CEA in patients with bone and liver metastases, and lower serum concentrations of tumor markers CA 15-3 and CEA in patients with metastasis to the lungs and lymph nodes.

A correlation between elevated serum levels of tumor markers CEA and CA 15-3 and the disease was shown by Colomer et al. (16). In their study, patients with multiple metastases had a higher proportion of elevated serum levels of tumor marker CA 15-3, compared to patients with metastasis to only one localization (81.2% compared to 51.4%).

The results of this study are similar to the results of other studies performed in the

world. In this study, taking into account the mammographic and ultrasound features of the changes to the breasts, that are in 72% of cases classified as BIRADS V, and in 28% of cases as BIRADS IV, and the values obtained of serum concentrations of tumor markers CA 15-3, it has been shown that tumor marker CA 15-3 has no diagnostic value in the diagnosis of breast cancer, except in exceptional cases of significantly elevated values of tumor marker CA 15-3, when used to find the localization of the primary tumor that has already spread to distant metastasis. We have shown that serum tumor marker CA 15-3 is not elevated in patients with histologically verified breast cancer, and in whom there is no proven presence of regional or distant metastases, but the values of serum concentrations of tumor marker CA 15-3 were significantly elevated in patients with verified breast cancer, axillary and distant metastasis, or associated metastases, and its concentration increases depending on the number of affected organs and organ systems, and on the dissemination of the underlying disease. However, in patients with verified breast cancer and metastases in the axillary lymph nodes, in as many as 64.5% of cases, the concentrations of the tumor marker CA 15-3 were not increased.

Conclusion

There is a significant correlation between serum levels of tumor marker CA 15-3 and the presence of metastasis, or the value of tumor marker CA 15-3 and the dissemination of the basic disease. It is certain that a minimally invasive diagnostic test, such as the determination of serum levels of tumor markers, would be very useful in the detection of breast cancer. However, the tumor marker CA 15-3 as such should not be used as it may be elevated in patients with benign changes in the breast, and normal in patients with the presence of primary breast cancer, and even in patients with proven breast cancer and verified metastases in the regional axillary lymph nodes. Mammography and ultrasound are proven effective diagnostic methods in the early detection of cancer (early stage disease) and this significantly affects the prognosis, the treatment, the quality of life and prolonging the life of patients.

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Review article

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Understanding wider environmental influences on mentoring: Towards an ecological model of mentoring in academic medicine

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Mentoring is a complex developmental relationship that contributes to individual growth and career advancement in different areas of human activity, including academic medicine. This article describes a broader environmental milieux in which mentoring occurs and considers the ways in which the environmental factors may affect the process and outcomes of mentoring. An ecological model of mentoring is proposed that takes into account various factors broadly operating at three contextual levels. The first is societal or "macro" level, which implies cultural, economic, and political factors. The second is institutional or "meso" level, consisting of a) system-related factors such as field and discipline characteristics, and government policies, and b) organization-related factors such as mentoring climate, reward structure, and work design. The third contextual level relates to intrapersonal and interpersonal characteristics of mentor-mentee dyads. If mentoring dyad is viewed as the focal point, societal and institutional levels may be labeled as "external", and personal level as "internal". The conceptual diversity and methodological challenges in the study of mentoring need to be acknowledged, but should not be an excuse to leave the external contextual elements out of the researchers' horizon, as they inevitably shape and modify the mentoring relationships. **Conclusion.** Model presented in this article offers a holistic view of mentoring in academic medicine that may help one comprehend and appreciate the complexity of influences on mentoring, and inform the future research agenda on this important topic.

Introduction

Mentoring is a complex developmental relationship that contributes to individual growth and career advancement (1). This social construct has been extensively investigated in different contexts and settings, including social work, education, business, medicine and health care (2-4). In academic medicine, mentoring was recognized to have an important influence on personal development, career choice and navigation, and research productivity (5).

Most of the mentoring research was focused on the intrapersonal and interpersonal factors affecting dyadic relationships. On the intrapersonal level, mentor-related variables such as mentoring schemas (6), mentoring style (7), motivation to mentor (8), and mentor's experience as protégé (1,

9) were suggested to have an impact on the development and quality of relationships. Mentee-related variables can be broadly categorized in resources (10) and needs (11). On the interpersonal level, several factors and domains have been suggested to influence the mentoring relationships: perceived similarity (12), frequency of interaction (12), relational competence (13), congruency of expectations (6), and cost-benefit assessment (14).

Mentoring relationships, however, do not occur isolated from their environment. In a systematic review of mentoring in academic medicine, authors concluded that "mentoring is inextricably situated in a social context and shaped by the institutional culture and climate" (15). It follows that an integrative model of mentoring, which I will call the ecological model, has to include three contextual levels – societal (or "macro"); institutional (or "meso"), which can be further divided into system- and organization-level; and personal (or "micro"), which includes intrapersonal and interpersonal variables (Figure 1).

If mentoring dyad is viewed as the focal point, societal and institutional levels may be labeled as "external", and personal level as "internal". The latter is empirically better explored than former and several theoretical models of what I call personal or internal level have been proposed by the researchers in medical setting (16, 17). Institutional and societal levels, on the other hand, still need a theoretical explication to inform and underpin further research efforts.

The term ecological mentoring has previously been described and used to denote an integrative, holistic or synthetic approach to mentoring, which takes into account elements that may operate at different levels (18, 19). Throughout this paper I will adopt this term and use it to conceptualize a model in which complex interplay of various factors operating at different levels may all affect mentorship. As for the definition of mentoring, I will consider it as a face-to-

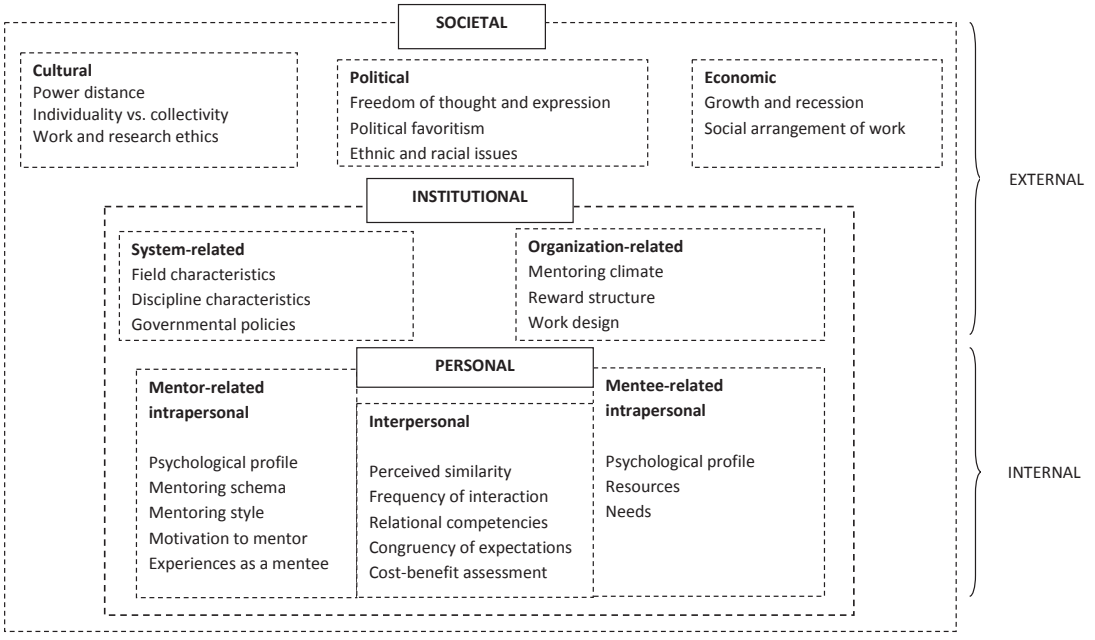

Figure 1 Integrative model of contextual levels and the related factors or domains that shape mentoring relationships. Dashed lines signify the "porousness" of the between-level borders: to some degree, levels overlap and affect each other. In a globalized and multicultural world, borders of the societal context are also "porous".

face, dyadic, and hierarchical relationship whose primary purpose is personal growth and professional development of the mentee, but whose beneficial impact extends to the mentor and a broader environment in which the relationship is embedded. In this relationship, which may be formally or informally initiated, mentors provide career and psychosocial functions to support the mentee. Mentoring implies a high level of commitment and continues over a longer period of time. This comprehensive definition is necessary to achieve conceptual clarity and avoid the confusion of mentoring with other types of developmental relationships, such as supervising or coaching (20).

The aim of this article is to describe a broader environmental milieux in which mentoring occurs and discuss the ways in which these environmental factors may affect the process and outcomes of mentoring.

INSTITUTIONAL CONTEXT

In this model, the term "institutional" refers to the system-related factors such as field- and discipline-characteristics and governmental policies, as well as the organization-related factors such as mentoring climate, reward system and work design in a particular institution (Figure 1).

System-related factors

Field characteristics

Academic medicine, considered here as a field within medicine, is a part of a wider scholarly environment, in which mentoring traditionally had a significant position within the apprenticeship model of graduate and professional education (21). Higher education in general consists of teaching and research activities, but academic medicine has an additional responsibility of providing health care to patients and populations. These three areas of activity are increasingly difficult to balance in a single career. Clinical care is burdened by demographic trend toward aging that results in increased severity and complexity of illnesses, while at the same time service expectations from patients are rising. Research has become highly competitive and resource-demanding. Educational reforms such as Bologna process in the European Union create additional burden of teaching, yet teaching activities are usually less valued in career assessment than research or clinical performance. The cumulative effect of these trends can have a detrimental impact on job satisfaction and diminish attractiveness of academic careers. Successful mentoring can provide psychosocial support, role modeling and career advice needed to overcome the challenges of working in academic medicine, yet it is exactly these challenges that are reducing the number and availability of mentors.

Discipline characteristics

Specific features of disciplines within academic medicine, such as recency, propulsiveness or interdisciplinarity, can produce different conditions that are more or less conducive for mentoring relationships. More recently developed disciplines, such as bioinformatics or conflict medicine, may be less likely to have a strong pool of potential mentors, as there was not much time for the development of many senior researchers and practitioners. Propulsive disciplines such as genetics and immunology may attract more resources than others, thus producing more opportunities for recruitment of new mentees, which in turn provides senior academics with more chances to try out and hone their mentoring skills. More interdisciplinary research areas and those that are dealing with more complex problems may require input from multiple mentors. Mentees in such disciplines may be more inclined to look for support from various sources, thus expanding their mentoring networks.

Differences in medical specialties may modulate the delivery of mentoring functions. In surgical disciplines the emphasis in mentoring may be on coaching to increase practical skills in performing operations. On the other hand, mentees in psychiatry may need more counseling, e.g. debriefing after dealing with emotionally demanding patients. Mentors in research-oriented disciplines such as genetics or pharmacology will generally be more able to provide a solid training in research activities, whereas mentors in clinically-oriented disciplines such as internal medicine, pediatrics or gynecology would be more helpful in fostering mentees' clinical performance and professional socialization.

General practice or family medicine builds the foundation of any healthcare system, yet its position as an academic discipline is sometimes challenged or poorly recognized. General practitioners work in the conditions of increased accountability with decreased professional autonomy, which contributes to demoralization and stress in the profession (16, 22, 23). Excessive workload of general practitioners in academic medicine may reduce their availability as mentors. General practices are usually operating in relative isolation from each other and even from other members of the health system, which limits the opportunities for academic interaction and initiation of mentoring relationships.

Government policies

Official government policies on healthcare, science and higher education constitute the most general formal framework in which mentoring relationships grow. Some policies are conducive for such growth – for example, when governments provide salaries for a certain number of research fellows who are adjoined to the ministry-sponsored research projects of senior members of academic community (24). This support facilitates recruitment of young scientists and their early connection with more experienced researchers who can potentially offer them a full range of mentoring functions. In reality, however, this potential is not always realized. Government-supported research projects may not be sufficiently discriminative and may lack a functioning system of monitoring and evaluation of performance (25). In such circumstances, mentoring relationships can be affected by a lack of political will or mechanisms to ensure full implementation of well-intended official policies.

Organization-related factors

Organizational culture

The effect of organizational culture is possibly the best explored and documented external-level element of the ecological model of mentoring. Department climate can influence values and attitudes of organizational members, often through the actions and role-modeling of mentors who assist their mentees as they are socialized into a community's practices. One manifestation of a developmental climate in institutions of academic medicine is the existence of formal mentoring programs, which represent a conscious use of faculty experience to develop students and early-career physicians. Formal mentoring programs have been initiated and reported in different medical institutions and settings, although their effectiveness has not been convincingly established due to descriptive nature of most of the reports (26).

Some research has indicated that formal mentoring is less effective than informal (27). The latter, of course, cannot be arranged or assigned. However, institutions may facilitate spontaneous development of mentoring by providing the structure, processes and expectations for such relation-

ships to occur. For example, they can offer workshops for students and junior faculty to help them build up the skills and competencies necessary to develop effective informal mentoring relationships. Other interventions may be directed towards the design of work.

Work design

In her seminal work on mentoring in business organizations, Kram suggested that the design of work, including its structure and processes, can facilitate or interfere with building relationships that provide mentoring functions (1). Although collaborative and team work is a common feature of academic medicine, both medical profession and academic community are characterized by hierarchical structures which can deter newcomers from attempts to establish more personal contact with those in senior positions. To overcome this obstacle, academic institutions can encourage interactions and communication between senior and junior faculty, and students, by establishing regular semi-formal meetings and journal clubs, or trying innovative approaches such as "speed-mentoring" events (28).

Development of long-term mentoring relationships between faculty and undergraduate medical students is often hindered by a disconnection between preclinical and clinical years of study, and continual course rotation. These challenges could be overcome by promoting students' longitudinal relationships with clinicians through continuity clinics and research projects (29) or by combining peer-to-peer mentoring with physician-to-student mentoring (30).

Work design can vary depending on the type of academic institution. Study conducted in a transition country has shown that the type of institution was associated with the success of research trainees: research institutes had a highest rate of mentees who completed their fellowships with a PhD degree; this rate was lower at the schools of medicine, and even lower at the university clinics (31). This can likely be explained by the primary mission of each type of institution, namely research, teaching, or clinical care.

Reward structure

Institutional expectations are reflected in the reward structure and criteria for promotion. In academic institutions, research productivity is often valued and rewarded more than educational excellence (32). This may be due to the fact that the number of published articles and obtained grants is more convenient to track than the quality of teaching. A complex developmental relationship such as mentoring is even more difficult to quantify than teaching. To limit this bias against educational activities and improve their mentoring climate, some institutions have established awards for outstanding mentorship (33). There are, however, some challenges in deciding about the best mentorship in an institution. Only a few instruments have been developed to assess the quality of mentoring and that mostly for research purposes (34). Someone's mentoring quality cannot be established by a popular vote, as much effective mentoring is informal, one-to-one interaction that occurs out of the horizon of most other institutional members. Furthermore, best mentors may not necessarily have more than one or a few mentees at any given time, so they cannot attract many votes. The rate of successfully mentored graduate students may be a long-term outcome more appropriate to assess the quality of academic mentoring, but this outcome fails to account for mentoring provided to undergraduate students and junior faculty.

Institutions may decide to openly reward participation in formal mentoring pro-

grams. Such a decision gives a clear signal about organizational expectations, which can result in some senior members volunteering for the mentoring role half-heartedly, only to meet the expectations. Less overt approaches may prove more beneficial, for example when department heads take the lead in accepting and working with mentees, thus championing formal mentoring programs.

SOCIETAL CONTEXT

All social interactions, including mentoring and other developmental relationships, are situated in a context shaped by cultural, economic and political factors.

Cultural factors

Culture comprises the ideas, beliefs, and knowledge that characterize a particular group of people. Cultural identity is most commonly conceptualized as nationality or ethnicity, but Chao and Moon pointed out that multiple cultural identities may arise from demographic, geographic, and associative features (35). Mentoring research has mostly addressed the demographic features such as gender and race as possible modifiers (13), often in relation to perceived similarity between the two actors in the relationship.

In his insightful discussion of the wider international perspective on mentoring, Clutterbuck emphasized two cultural dimensions as particularly relevant – *power distance* and *individuality* (7). The power distance or stance towards authority affects the mentees' willingness to challenge what they are told. For example, a suggestion that mentees should be selective in accepting advice from mentor (36) is typical for a low power distance culture. Power distance may also influence mentees' agility in seeking informal mentors. Consequently, formal mentoring programs may be especially beneficial in cultures with a high power distance. This cultural dimension may also make it easy or difficult for either mentor or mentee to express emotions and permit vulnerability, thus affecting the provision of psychosocial mentoring functions. Power distance is related to performance orientation, a cultural variable defined as the degree to which an organization or society encourages and rewards group members for performance improvement and excellence. In an early example of a study empirically exploring cultural influences on mentoring, Gentry and colleagues used a multinational sample of practicing managers to prove their hypothesis that performance orientation is a significant cross-level moderator of the relationship between career-related mentoring and performance (37). A more recent study in the organizational setting showed that power distance weakens the impact of career and psychosocial mentoring on the motivation of subordinates (38).

Individuality is the other dimension suggested by Clutterbuck as important for understanding mentoring in different cultural contexts (7). In cultures that emphasize individuality, rather than collectivity, each individual is considered chiefly responsible for developing and maintaining their own developmental relationships or – in the words of participants of a Canadian study – taking "the driver's seat" (39). Highly individualistic cultures may inhibit mentors' responsiveness to mentees' needs and devalue efforts put in the development of others.

Work ethics is another important cultural factor that may influence the development and nature of mentoring relationships in academic medicine. Through their role-modeling, mentors perpetuate and support certain work ethics, which may or may not be compatible with the standards and values of academic medicine internationally. An important concept related to the issue of work ethics is *research integrity*. Biomedicine

is a research-intensive field of science and much of this research is carried out at the academic institutions. High research productivity in biomedicine can be explained by a considerable funding of medicine- and health-related research, but also by a strong pressure to "publish or perish". Such a pressure may push some members of academic community towards scientific misconduct, especially if fraudulent behavior is widespread and tacitly tolerated in a society. Social norms such as the rule of law, corruption and democratic accountability differ across cultural regions of the world (40). These social norms may reflect in the inclination of mentors in academic medicine to commit or tolerate scientific misconduct. Both through their role-modeling and direct communication, mentors provide information about the ethical behaviors, moral obligations, and codes or regulations to which their mentees are expected to adhere within the academic community.

Economic factors

Economy may shape the nature and role of mentoring in human society in profound, if not immediately obvious ways. Savickas suggested that mentoring came into focus as "a societal response to the reorganization of the work world occasioned by the global economy" (41). Work of the 21st century is characterized by the fragmentation and lack of security, with assignments and projects replacing permanent jobs and careers. Such a social arrangement of work requires constant negotiation of transitions, life-long learning, and continuous progression of developmental relationships, including mentoring. It is therefore not surprising that the concept of mentoring networks or mentoring constellations rapidly developed only during the last 15 years (42, 43).

In many respects, today's academic medicine bears the marks of contemporary social arrangement of work. This is visible, for example, in temporary nature of research fellowships and postdoctoral positions, requirement of mobility, need to juggle the "triple threat" of an academic career, and permanent evaluation of performance and output. Such an arrangement of work may increase stress, tensions (including problems in work-family balance), job insecurity, and role ambiguity among physicians in academic medicine, producing a need for additional psychosocial and career support by mentors. The same socio-economic pressures, however, are also acting on the side of mentors, limiting their availability and capacity to provide the needed support. Anxiety over keeping jobs and obtaining research grants drains the mentors' emotional energy necessary for building positive developmental relationships. In the business context, Allen and colleagues found that mentors are reluctant to invest their time and energy in developing mentoring relationships in a turbulent job environment where job security is an issue (9). In the context of academic medicine, it has been observed that economic crisis and job availability affect career choices of medical students (44). It is conceivable that concerns about job insecurity and wage reduction also have an impact on the willingness of senior faculty and physicians to commit themselves to mentoring relationships.

Political factors

Political factors refer to the official political system in a country or to the more or less unofficial "politics" and policies in academic institutions. In communist regimes of the second half of the 20th century, freedom of thought and expression was relatively suppressed and the single-party political system prevented the development of pluralistic and democratic societies. Transition countries have changed their political systems,

but the underlying values and habits of their citizens, including many of the senior academics, are shaped by the experiences of living under totalitarian political regimes. Due to these formative experiences, some mentors in transition countries never learned to speak truth to the power or even to participate in a truly democratic discourse. Consequently, they are ill-equipped to help their junior colleagues become "thoughtful, questioning professionals in regard to the society around them", which is an important responsibility of mentors in academic medicine (45). It must be emphasized that even in countries with a long-time democratic history, there is an important role of mentors in enabling younger generations of academic physicians to critically address the present position of medical profession at the crux of power, knowledge and technology (45).

In totalitarian political systems, eligibility based on political or ethnic affiliation was a common prerequisite for upward mobility in many state institutions, including academic ones. Political constraints inevitably affected all spheres of social life, including mentoring relationships, and made a fertile soil for the growth of political favoritism. With the change of political system from totalitarism to democracy, some progress towards meritocracy has been achieved, but the role of favoritism is far from gone. The affiliation to a political party, especially if it is the ruling one, may be of help, but even more important is the affiliation (or "connections") to an informal "party" or "club" that controls the key institutional factors, such as access to funding or promotion (46). Thus, having a mentor from within the ruling "party" may facilitate career progression on the academic ladder, whereas choosing a mentor that is in the opposition to the ruling "party" may result in career difficulties or even drop-out from academic medicine.

In some countries, social and political developments throughout the history have led to certain racial and ethnic minority groups being underrepresented in the academy, relative to the overall population. There is an increasing number of formal mentoring programs developed in academic institutions to address unique challenges faced by underrepresented minority faculty (47). There is some evidence that mentoring and faculty development programs for minority faculty can increase retention, academic productivity and promotion rates for this group (47, 48).

IMPLICATIONS FOR RESEARCH

Quantitative research of mentoring in academic medicine has mostly dealt with prevalence and outcomes, and was found to be limited by cross-sectional design of the majority of studies (5). Mentoring was less frequently explored by qualitative research methodologies, which primarily addressed the personal contextual level of mentoring relationships (15). Organizational influences were mostly described in reports of formal mentoring programs, which were found to be poorly evaluated (26). A relatively underdeveloped research base in academic medicine can partly be explained by the methodological and conceptual challenges in studying complex developmental relationships such as mentoring (20, 34). The challenge of complexity becomes even greater when system- or societal-level influences on mentoring are taken into account.

The conceptual diversity and methodological challenges need to be acknowledged, but should not be an excuse to leave the external contextual elements out of the researchers' horizon, as they inevitably shape and modify the mentoring relationships. Failing to recognize the role of external context may result in a biased interpretation of the literature. For example, a wealth of studies and scholarly articles on mentoring, produced across academic disciplines and fields, may easily create a perception of

mentoring as a well-explored and developed construct. However, most of the existing literature originates from the western developed countries (3, 5, 15). Such geographic homogeneity or asymmetry may result in a thorough, but one-sided understanding of mentoring. Dougherty and Dreher point out that "programmatic research is needed to better understand whether the association between mentoring and career outcomes – most often studied within the context of U.S. culture – will generalize to national cultures that differ from the United States" (34).

To bring such "programmatic research" to reality, academic medicine could make use of its well-established international research networks and collaborations to engage academic institutions across countries in multi-center studies of mentoring. Such studies should be carefully designed to control for various contextual variables. Theoretical lens and validated instruments should be borrowed from other academic fields such as sociology, anthropology, economics and political sciences. Use of interdisciplinary approach to study of mentoring in academic medicine will enhance our ability to elucidate and better understand this important developmental relationship.

Conclusion

Mentoring is a desirable and beneficial, albeit demanding and sometimes even challenging relationship for people working in academic medicine. It is not only in their best interest, but also in the interest of their institutions and broader communities to better understand the mentoring dynamics and processes. In contemporary academic world, issues of quality in education and research have gained a prominence and raised attention to various factors affecting the quality. Mentoring is a recognized tool for improving the quality of academic medicine. However, proper understanding of such an important and complex developmental relationship cannot be achieved without looking beyond the persons directly involved in it. As the influence of academic medicine expands in a wide range of societal contexts, so does the society have an inevitable impact on the conditions and relationships within the academic medicine. Model presented in this article offers a holistic view of mentoring that may help one comprehend and appreciate the complexity of influences on mentoring, and inform the future research agenda on this topic.

What is already known on this topic

- *Mentoring is a developmental relationship that has been studied extensively in different contexts and settings, including academic medicine. The previous research has mostly focused on intrapersonal (e.g. characteristics of mentor or mentee) and interpersonal factors (e.g. dynamics of mentor-mentee relationship) that influence mentoring. There were very few attempts to explore external contextual factors affecting mentoring relationship, possibly due to a lack of theoretical explication to inform and underpin such research.*

What this study adds

- *This article provides a comprehensive conceptual framework for future research by explicating institutional and societal context of mentoring in academic medicine. An ecological model of mentoring is proposed that takes into account relevant factors on micro-, meso- and macro level.*

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Cochrane and its prospects in Bosnia and Herzegovina: Relying on Cochrane Croatia

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In this article we describe Cochrane and its products: Cochrane systematic reviews (CSRs) and other Cochrane evidence. Cochrane is a unique, international, non-profit organisation that offers health care providers, health care consumers and other decision makers unbiased and highly reliable information on health, which is pivotal for conscientious and responsible decision making in overall healthcare. Cochrane offers the highest ranked evidence in Evidence Based Medicine (EBM) – systematic reviews. Currently, CSRs are freely available in BH, and therefore, they ought to be widely used, and understood. We will present the new *Cochrane Strategy to 2020*, which was the main topic of the 6th Croatian Cochrane Symposium (CroCoS), as well as explore prospects for spreading Cochrane activities to Bosnia and Herzegovina (BH), through collaboration with Cochrane Croatia. BH has no officially organized Cochrane activity, as yet. We hope that this article will raise awareness about Cochrane in BH, help promote its activities, and deepen the existing collaboration with Cochrane Croatia. There are already some changes being introduced concerning Cochrane – at least, in one half, the Federation of BH (FBH). Two documents symbolising official recognition of policy changes towards Cochrane have recently been published in the *Official Gazette of FBH*. **Conclusion.** Since founding a BH Cochrane Branch would be costly and difficult to achieve in a complicated environment, such as the one we have, BH could use the good will, experience, knowledge, and translated educational, training and web materials of Cochrane Croatia, particularly given the language similarities, to promote evidence based medicine in BH.

Introduction

The awareness of the importance of Evidence-based Medicine (EBM) and of Cochrane is growing in Bosnia and Herzegovina (BH). However, BH does not have an official group of Cochrane or any organised Cochrane-related activities. In this article, we stress the importance of Cochrane's legacy and prospects for expanding its activities in BH, with a particular focus on Cochrane Croatia, which was founded in 2008 and since then has become a strong partner to all stakeholders in that country - decision makers, physicians, and most recently, patients. Their knowledge, experience and good will towards collaboration ought to be used in BH. For the time being, the most important step is to raise physicians' awareness of EBM and Cochrane in BH.

The highlights of the 6thAnnual Croatian Cochrane Symposium (CroCoS) will be presented in this paper as well. Finally, we will give a blueprint for the future of Cochrane activities in BH.

About Cochrane and Its Greatest Treasure: the *Cochrane Database of Systematic Reviews (CDSR)*

Cochrane is a unique, international, nonprofit organisation that offers health care providers, health care consumers and other decision makers unbiased and highly reliable information on health, which is pivotal for conscientious and responsible decision making in overall healthcare.

Cochrane stands at the forefront of the EBM movement (1). As defined by Sackett et al., EBM is the "conscientious, explicit and judicious use of currently best evidence in making decisions about the care of individual patients and involves integrating individual clinical expertise with the best available clinical evidence and patient preferences"(2). The ″best evidence″ is generally accepted to be that arising from systematic reviews of randomised controlled trials (2), which is what Cochrane has been producing for over two decades.

Cochrane was founded as The Cochrane Collaboration in 1993 and named in honour of the British epidemiologist Archibald (Archie) Cochrane, who in 1979 wrote: "It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials″ (3). The Collaboration has grown enormously over the last two decades and in January this year it changed its name to 'Cochrane'. It is now a network of over 34,000 individuals, mostly volunteer authors, who work hard to produce systematic reviews (4). These individuals are supported by a network of Cochrane support groups, including centres, branches, review groups and fields. Cochrane's main product is the *Cochrane Database of Systematic Reviews (CDSR)*, a central part of *The Cochrane Library*. *The Cochrane Library* is a collection of six databases that contain different types of high-quality, independent evidence to inform healthcare decision-making: Cochrane Database of Systematic Reviews (CDSR), *Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register (CMR),Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (EED)*, and a seventh database that provides information about Cochrane groups, called *About The Cochrane Collaboration*. *The Cochrane Library* is a journal published by John Willey and Sons, with an impact factor in 2013 of 5.939 (5). The total number of citations received by the *CDSR* is the 6th highest in the General & Internal Medicine category of scientific journals. In 2013, only the top 3 ranked journals (*NEJM, Lancet, JAMA*) received more citations than *CDSR* (6). *CDSR Issue 11*, published in 2014, comprises 6180 published reviews and 2352 protocols, totalling 8532 records (7), and reaching 8636, the total number of records in 2015 (8).

Thanks to its middle income status, the whole territory of BH has *one-click free access* provided by Internet Protocol (IP) recognition (no individual login), meaning that all IP addresses from BH have unrestricted access to *The Cochrane Library* (9). Every user from BH can download the full text of every Cochrane Systematic Review (*CSR)* from the *CDSR,* which is a great convenience. This status is reviewed every January.

Cochrane Systematic Reviews

Systematic reviews synthesise all available clinical research on a particular topic, and therefore systematic reviews of randomised

controlled trials (RCT) represent the highest level of evidence (10). They are the most rigorous way of determining whether a cause-effect relationship exists between an intervention and pre-determined outcomes (11). Double-blind placebo-controlled randomised trials (RCTs) are regarded as the gold standard tests in clinical research. Their strength lies in randomisation - random assignment to a study or a control group minimises all known and unknown factors that could influence the final results. In a systematic review, the data from more RCTs are combined, which increases the strength of evidence. Conducting a *Cochrane Systematic Review (CSR)* is a scientific investigation in itself, so-called secondary research, with the original studies being its "subjects" (12).

Each systematic review starts with a clinical question; the one proven to be still without a definite answer. After choosing the right question, a protocol is written. It is a peer-reviewed, predefined plan for conducting a review and it specifies the objectives, inclusion criteria, methods for study identification and selection, methods for assessing risk of bias in included studies, and outcomes of interest. Transparency and methodological rigour in producing a *CSR* are what makes them the 'gold standard' among systematic reviews. Since the protocol makes all these data available for public inspection, it functions as a public record explaining how the review authors intend to answer their research question (13).

After assessing for study validity, results of different independent studies are analysed in a process called a meta-analysis which represents a statistical summary of the results of the individual studies. Integrating numerical data from several primary studies that are related to the same question provides a more precise estimate of the intervention's effect. Yet, it is not always possible to conduct a meta-analysis in a systematic review, because if the study interventions or measured outcomes show considerable heterogeneity, a meta-analysis cannot be done (13).

There are five types of *CSRs*. The most common are *intervention CSRs,* which assess the benefits and harms of interventions used in healthcare and health policy. *Methodology CSRs* are prepared by a methodology group and address issues relevant to how systematic reviews and clinical trials are conducted and reported. The remaining types of CSRs are as follows: *diagnostic test accuracy reviews* (aassess how well a diagnostic test performs in diagnosing and detecting a particular disease), *qualitative reviews* (synthesize qualitative evidence to address questions on aspects other than effectiveness), and *prognosis reviews* (address the probable course or future outcomes of people with a health problem) (14).

Cochrane Croatia: involving physicians, medical students and patients

With a goal to publicly advocate the use of Cochrane evidence in everyday health care decision making and to assist authors in producing *CSRs*, a Croatian branch of the Italian Cochrane Centre was established at the University of Split School of Medicine in 2008 (15). The Croatian Cochrane Branch is the reference centre for all surrounding countries, including BH, which would like to promote EBM and become involved in the activities of Cochrane.

One of the first activities conducted by Cochrane Croatia was a nation-wide study among physicians in Croatia about their awareness and use of EBM databases and The *Cochrane Library*. This study indicated that a third of the respondents had heard about The *Cochrane Library* and 10% of the respondents used the *Library* and read systematic reviews (16). In its conclusion the study highlighted that such a low level of awareness of EBM and The *Cochrane Library* warranted educational interven-

tions for physicians, for the benefit of overall healthcare for patients in Croatia (16). Consequently, the majority of initiatives initially undertaken by Cochrane Croatia were focused on healthcare workers, mostly physicians. The first Croatian Cochrane Symposium was organised in 2009, and the same year a regular column presenting *CSRs* started appearing in *the Medical Gazette*, the official journal of Croatian Medical Chamber. Various workshops and lectures for physicians were organized in hospitals and during symposia.

Another significant effort has been made in raising awareness of EBM and Cochrane in Croatia, this time among medical and health sciences students. In 2010 the Medical School in Split introduced a mandatory, vertically integrated course in research methodology into medical and dental curricula. The requests for curricular changes issued by the European Commission were answered by shaping the Split curricula into an original blend of traditional pre-clinical and clinical subjects with several vertically integrated subjects focusing on mastering clinical skills, professional attitudes, information management and critical, as well as evidence-based reasoning and decision making (17). Marušić et al. have found that the new course succeeded in increasing students' knowledge and skills for critical thinking and EBM, and prepared them for life-long learning in medicine (18).

Students at the University of Split School of Medicine are taught EBM from the first day of their studies, but there is a need to enhance their skills in evidence-searching and critical appraisal of the evidence in clinical practice, with real patients. As revealed by Vrdoljak et al. (19), teaching final-year students the practical use of EBM in a general practitioner's office might play an important role in the students' professional development. It may positively influence the quality of their future work, making EBM a basis for their life-long learning.

Practical Evidence About/For Real Life Situations (PEARLS), published by Cochrane Primary Health Field, are intended to make decision making even faster, easier and more adjusted to suit the needs of primary care practitioners. *PEARLS* have been regularly translated by members and collaborators of Cochrane Croatia since 2013.

However, the growing awareness of a need to shift focus from health care professionals to the lay consumers of evidence has been recognised by Cochrane Croatia as well. Patients should be involved in the decision-making process as equal partners. They should be able to access and get high-quality information about health in general and medical evidence should serve them directly. Therefore, since 2012 several initiatives have already been implemented in order to engage consumers in the activities of Cochrane Croatia. This idea was supported at the national level by Croatian Ministry of Science, Education and Sports, which awarded five grants to Cochrane Croatia for the ″popularisation of science″. Three of them have been used for engaging patient groups in selecting and translating *Plain Language Summaries (PLSs)* of *CSRs* into Croatian. A PLS is an overview of the findings of a Cochrane Systematic Review written in a language appropriate for patients and family members. The summary contains a brief statement of the significance of the review, the main findings of the professional review, preferably including the number of studies evaluated and number of total participants, comments on any adverse effects and limitations of the review. Thus, in 2012, Croatian became the sixth language in the world, after Spanish, French, Portuguese, Chinese and Arabic, in which translated *PLS* were made available. Croatian *PLSs* are published on the Croatian version of the Cochrane web site: http://www.cochrane.org/hr/health-evidence.

Soon after, Cochrane Croatia recognised the increasingly important role of social networks in Croatian society and their potential in disseminating Cochrane evidence and other EBM-related information. As a result, in March 2013 a Facebook page called *"Croatian Cochrane Branch"* was opened and it currently has 1,902 ″likes″ (as of February 26, 2015).

One grant for the popularisation of science was invested in translation of the book "*Testing Treatments*", written by Imogen Evans, Hazel Thornton, Iain Chalmers and Paul Glasziou. The book-related website '*Testing Treatments Interactive*' has also been translated into Croatian and offers its visitors an opportunity to read the book free of charge at http://hr.testingtreatments.org/procitajte-knjigu-gdje-su-dokazi/.

Finally, since it has become clear that more emphasis should be put on education of the lay audience on the uselessness of many alternative and complementary therapies that are offered by 'quacks' in the market, the fifth grant for popularization of science is being used for the development of a website called *"Evidence in medicine"*(http://dokaziumedicini.hr/), where anybody can ask questions about effectiveness and safety of interventions in medicine, and a group of scientists respond to these questions based on the best evidence available.

In September 2014, a nationwide survey of the knowledge and usage of EBM and *CSRs* was conducted among Croatian urban and rural patients visiting their family doctors on a regular basis, and its results are expected to be available in 2015. The survey results will show whether educational initiatives conducted by Cochrane Croatia have reached their intended consumer audience, and will provide guidance for the future work aimed towards consumers of Cochrane evidence.

The Croatian Cochrane Symposium (CroCoS) is traditionally held at the Medical School in Split, every year in spring time. The 6th CroCoS was held on Friday 6th June 2014, on the topic *'Better Evidence for a Better Future: Cochrane's Strategy to 2020'* and it consisted of eight presentations, two parallel round tables and two concurrent workshops for future/current Cochrane authors.

Mark Wilson, Chief Executive Officer (CEO) of Cochrane, spoke on the organization's current position and strategic plans, emphasizing the fact that Cochrane is a unique, innovative and global independent network of evidence-based medicine enthusiasts and a recognised leader in its field, with a global reputation for quality and integrity. However, he also said it is necessary to transform Cochrane into a more effective and sustainable organisation in order for it to achieve its long-term goals. Activities of Cochrane must be focused on advocating high-quality, relevant and up-to-date evidence that will be useful and accessible to everybody, everywhere in the world, to enable making informed decisions in health care.

Dr. Irena Zakarija-Grković, Co-Director of Cochrane Croatia, spoke about the power of partnerships built within the Croatian Cochrane Network. This network has already included five professional societies and five patients' associations as official partners. One of the professional associations is the Medical Chamber of Zenica-Doboj Canton from BH. The aim of the network is to connect with various partner institutions, professional societies and patient organisations which are interested in promoting evidence-based medicine.

Professor Ana Marušić, the Research Coordinator of Cochrane Croatia, spoke about different ways of using Cochrane evidence to create basic national drug lists. She presented the results of a study in which the Croatian Basic List of Medicines and the World Health Organization Model List of Essential Medicines (WHO EML) were compared. This study found that there are medicines on the Croatian Basic List of Medicines which

were rejected by WHO's EML Committee, mostly due to lack of evidence for their effectiveness (20). In this study they used *CSRs* as surrogate markers of drug effectiveness. Professor Marušić also presented the calculated costs of using the drugs which have been rejected by the WHO.

Cochrane's Coming of Age

In March 2013, more than 200 Cochrane leaders from all over the world met in Oxford, UK, to commemorate the first 20 years of the Cochrane Collaboration and to work together on a strategic framework for the next several years. This task, led by Cochrane's CEO, Mark Wilson, incorporated an analysis of the organisation's current strategic framework, a series of policy and strategy documents developed by Cochrane contributors from a 2008-9 Strategic Review, and wide consultations and feedback from contributors. A first draft of the new Cochrane Strategy was released for contributors and selected external stakeholders in July 2013, and following extensive feedback and numerous meetings, a final draft was presented and accepted by the organisation's members at the 2013 Annual General Meeting, on 21st September, in Quebec City, Canada, at the 21st Cochrane Colloquium.

The Cochrane Collaboration's first 20 years have been an astonishing success, with Cochrane significantly contributing to the mainstream acceptance of "Evidence-Based Medicine", and becoming the acknowledged, global leader in systematic review production. In 2008, there were fewer than 10,000 authors; today there are more than 22,400 active registered authors of *CSRs*, including those 42 from Croatia. There has been dramatic growth in the organisational infrastructure with currently 14 Regional Centres and 24 Branches (including the Croatian Cochrane Branch), 53 Review Groups, 16 Methods Groups and 12 thematic Fields and Networks. With the increasing number of authors, Cochrane review production has grown exponentially over the years, with more than 8,100 full *CSRs* and Protocols in the *CDSR*. The rising awareness and use of Cochrane evidence has followed, with over 7.4 million full-text downloads and 13.5 million abstract page views in 2013. In addition, another 4,181,131 million page views of *Cochrane Summaries* were recorded that same year (21).

Throughout this journey, Cochrane has had to face numerous challenges. These included managing the complex *CSR* production process, or more specifically, prioritising reviews and updates of reviews, training authors, providing review groups with adequate support, facing increasingly long review production processes, maintaining the quality of reviews and stimulating authors to complete and update reviews. Other constant challenges are decreasing the knowledge translation gap, improving the "User Experience", allowing global access to Cochrane content, securing funds for Cochrane activities, involving contributors from non-English speaking and low and middle income countries and facing rising competition. Cochrane's response to these challenges is its *Strategy to 2020*.

Cochrane's Strategy to 2020

The four main goals in *Strategy to 2020* represent the desired endpoints for achieving the organisation's mission (22). Specific objectives describing the ways in which goals will be achieved and activities conducted have been set up for each goal.

Goal one is to produce evidence faster and more effectively, without compromising on quality. The objectives include quality assurance, relevance, timeliness, wide coverage, pioneering methods and efficient production. In 2014 alone, SMART (Specific, Measurable, Attainable, Relevant and Time-

Bound) targets for goal one were set up in order to develop a list of approximately 200 new "high-priority" and "up-to-date" CSRs (that was published in January 2015 on the Cochrane.org website), as well as to improve production processes by implementing an author support tool and establishing a strategy for reducing review production time by 30 percent.

Goal two focuses on the users of Cochrane evidence, with the aim of making Cochrane content accessible to everyone, anytime and anywhere in the world, in a format that is user-centred. Cochrane will strive for a greater understanding of the end-users' experience with and their actual need for Cochrane evidence. A comprehensive translation strategy is already underway, aiming to make as much Cochrane content available in as many languages as possible, with at least key content translated into all WHO official languages by 2020 the latest. Cochrane Croatia is also playing a small but significant role in the translation of *Cochrane PLSs* and Cochrane launched a Croatian-language version of its Cochrane.org website in 2015. With the support of the Croatian Ministry of Science, Education and Sports, Cochrane Croatia, together with its growing team of collaborators, has translated over 700 *PLSs*, making quality evidence accessible to all citizens of Croatia and other neighbouring countries. Currently, full texts of *CSRs* are available only 12 months after their publication and by 2020 Cochrane aims to make all of its reviews available. Once a review is published, it risks getting forgotten if not properly disseminated, and because of that Cochrane has already incorporated in its *Strategy* various plans on how to build a dissemination framework into editorial process of *CSRs* to ensure that every review gets its own dissemination plan created to meet the needs of the targeted users.

Goal three of the *Strategy* is set up to make Cochrane a recognisable "go to" place for EBM. This will be achieved by creating an overarching, recognisable "Cochrane" brand; building greater recognition of the role of Cochrane as an essential link between primary research and health decision-making; advocating for evidence-informed health care and the uptake of synthesized research evidence in health policy making and services planning; promoting high-quality primary research which answers real world health questions and improves the evidence base upon which *CSRs* are built; by campaigning for transparency and integrity in scientific conduct; and by building international and local partnerships.

Finally, for all of these ambitious plans to be achieved, it is required to have an effective and sustainable organisation (**Goal 4**). Cochrane is committed to being inclusive and open, global and diverse, financially strong, efficiently run, investing in people, transparently governed and environmentally responsible. It is also planning to introduce a membership scheme in order to improve its organisational cohesiveness and reduce possible barriers to participation. A training and professional development strategy is underway, as well as a review of Cochrane's governance structure and processes. *Strategy to 2020* encompasses a program on how to identify, mentor and train future leaders of the organisation. Cochrane is rapidly increasing the number of women in leadership positions: both of its Co-Chairs of the organization's Steering Group (Governing Board) are female as are over 60% of the present Steering Group. It is also committed to increasing diversity in other ways, to have more than 50% of its leaders originating from non-English speaking countries by 2020.

Strategy to 2020 is an opportunity to create a world of improved health by producing and promoting use of high-quality evidence informed research, and then making its results usable and accessible to anyone who needs it. Through collaboration with Co-

chrane Croatia, BH researches, academics, health professionals and others involved in health research have an opportunity to join Cochrane on this exciting journey.

Prospects of Cochrane in BH– "Cochranising" BH: A wave from the city of Diocletian

In order to analyse prospects of Cochrane in BH, one first has to understand BH's unique political situation. BH comprises two autonomous entities: the FBH and Republic of Srpska, with another region, the Brčko District BH, governed by local authorities. Saying that BH is decentralised would be a large understatement. In BH, there are less than 4 million people (23) and furthermore, 4 levels of power (municipal, cantonal, federal and state) with as many institutions governing. In such a decentralised environment, trying to organise any kind of institutional Cochrane entity is almost impossible. Is it necessary at all?

During the 6th CroCoS, Mark Wilson, Cochrane's CEO, stressed that the organization was committed to establishing flexible structures that best meet the needs and contexts of different countries, regions and parts of the world. He suggested that networks based on multiple hubs of people working on Cochrane activities in different places may work well for BH and the wider region. Founding an official entity in every country is a huge burden for any organisation, especially for those that operate and rely primarily on voluntary efforts.

When it comes to BH, there are already some changes being introduced concerning Cochrane – at least, in one half, the FBH. Two documents symbolising official recognition of policy changes towards Cochrane have recently been published in the *Official Gazette of FBH*. The first document was published on 7th July 2014, only a month after the 6th CroCoS was held (24). In it, the ability of proper use of The *Cochrane Library* was listed as one of the essential skills required for clinical pharmacology trainees to have developed in their training program curriculum. The second important document was also published in the *Official Gazette of FBH* on 15th October 2014, in which *The Cochrane Library* was classified as an officially acknowledged source of information for another emerging issue in BH: Health Technology Assessment (HTA) (25).

In Croatia, there are many good examples of how to raise awareness and enhance the usage of reviews offered by Cochrane that should be followed. In Zenica-Doboj Canton, there is already research being conducted on evaluating attitudes and awareness of physicians towards EBM and Cochrane. Also, it is important that Cochrane's strict methodology is recognised as the ″gold standard″ in conducting systematic reviews: the first BH authors to use Cochrane methodology in performing a systematic review were Salkić at al. (26), although the review was not published in Cochrane Library. Another important step is to gather all Cochrane sympathisers in BH. We could again follow the example of Cochrane Croatia in its use of social media in order to reach the general population. It would be a very useful yet inexpensive way to reach as many health care professionals and health care users as possible, but some kind of organised approach will be needed, without any doubt. It would be helpful if an institution could be found to provide at least a part time administrator, educator, health professional or researcher - a person and a place to gather and distribute information on Cochrane's BH activities.

Integrating a mandatory course on research methodology into medical schools' curriculum is of primary importance. Integrating Cochrane evidence such as Cochrane Clinical Answers into GPs' education is highly desirable. In order to over-

come the language barrier when using English sources, which is a serious problem for most senior physicians, multicultural and multilingual BH should again rely on collaboration with its neighbouring countries. As mentioned above, Cochrane Croatia is currently conducting a translation project, financed by government grants and aimed at translating Cochrane *PLSs*, among other materials, into Croatian. Croatian is one of three official languages in BH, and the differences between Croatian, on the one hand, and Bosnian and Serbian, on the other, are not an obstacle for understanding abstracts in Croatian by people speaking these other two constitutive BH languages. Translated *PLSs* could serve patients and their health care providers. Other steps in collaborating with Cochrane Croatia have also been undertaken. The Medical Chamber of Zenica-Doboj Canton has become an official partner of Cochrane Croatia; the Chamber representatives attended the first introductory and priority setting meeting for Cochrane partners at this year's Croatian Cochrane Symposium. We believe that this step could be the first in making a Cochrane nucleus in BH. In addition, we have arranged everything to make the online course on systematic reviews, translated and prepared by Cochrane Croatia, available to all BH doctors, with CME points included.

Let us collaborate together and overcome all the boundaries that politics have forced upon us (ethnic, territorial, organisational) so that we can create a society in which patients and health care users are enabled to access high-quality, evidence-based information on health interventions. Last, but not least, we should aim to overcome barriers largely nourished by us, in the form of inter-specialty intolerance. Together, as citizens dedicated to EBM, we can change our world for the better.

Conclusion

Awareness of the importance of Cochrane, a synonym for evidence-based health care- is emerging in BH. Croatian Cochrane is pivotal for spreading Cochrane activities in BH. BH could benefit from using Cochrane Croatia's experience, good will and translated materials to establish Cochrane's position in BH. There is a need for a Cochrane Hub in BH.

What is already known on this topic

- *Cochrane (formerly The Cochrane Collaboration) was founded in 1993. Cochrane Croatia, a branch of the Italian Cochrane Centre, was founded in 2008 as a voluntary, non-profit organisation based at the University of Split School of Medicine as part of the Croatian Centre for Global Health. Its main roles are production of systematic reviews, promotion of evidence-based medicine and dissemination of Cochrane evidence throughout South East Europe.*

What this study adds

- *This paper presents the new* Cochrane Strategy to 2020*, and highlights from the 6th Croatian Cochrane Symposium (CroCoS). Also, in this paper we propose a blueprint for future as Cochrane-related activities in Bosnia and Herzegovina.*

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Postgraduate studies (1978-1985) at the Medical Faculty of the University of Tuzla, Tuzla, Bosnia and Herzegovina*

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The Postgraduate studies (PS) at the Medical Faculty (MF) of the University of Tuzla (UT) were founded with the aim of training future staff of the MF in scientific research work. The course lasted four semesters. Up to 1986, classes were attended by five generations or 141 postgraduate students, and 57 of them received their Master's degree (MSc's). Classes were held every week on Fridays and Saturdays. One part of the classes was taught at the MF in Szeged (Hungary). Besides teachers from the UT, classes were also taught by teachers from other universities from the former Yugoslavia and abroad. The most important textbooks were: *Cell and Molecular Biology* by de Robertisa, *Mathematics and statistics for use in pharmacy, biology, and chemistry by* Saunders & Fleming, and *Kako se pišu saopštenja o medicinskim istraživanjima* (How to write reports of medical research) by Rajko Igić. Searching the index base Pub Med at the end of 2014, by the surnames and initials of the names of the 57 masters, we found that they had published 14 articles before completing their MSc's and 821 articles after completing their Master of Science. Later, 35 masters received PhDs and were appointed assistant professors, and later they were also appointed to higher ranks. **Conclusion:** Looking at the results of the PS, MF of the UT in the above mentioned period, it can be said that the PS was the place where the formation began of the future scientific and teaching staff of the MF in Tuzla.

Introduction

The Faculty of Medicine in Tuzla was founded in 1976 and already in 1978, on the basis of a proposed study on founding a post-graduate course and a motion by the Faculty Board, at its session on 15 October 1978 the faculty council rendered a decision to launch a post-graduate study course (PS) (1). The aim of founding this course was to train future staff of the medical faculty in scientific research work in the field of pre-clinical and clinical disciplines (2). The curriculum and course programme (3) were in many ways original and significantly different from the curricula of other such courses in the former Yugoslavia. While it was being drawn up, account was taken of the fact that doctors and experts in the field of related branches of biomedicine who wanted to work in research

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should be acquainted with the necessary knowledge of scientific research work, as seen in acquisition of knowledge of English language, cell biology, biostatistics, research methodology and publication. The course lasted 4 semesters, during which the following subjects were taught: English language I and II, Biostatistics I and II, General Methodology of Scientific Research Work, Cell Biology, Medical Writing I and II, Selected Medical Research, Ideas in Biomedical Sciences, Medical Science and Civil Defence, Optional Subject, Creation of Master of Science (MSc) Thesis Project, and MSc Thesis. The fourth and final semester was planned for drawing up the project and writing the MSc thesis. The administrator of the course from its foundation and until 1985 was Prof. Dr. Rajko Igić, at that time the pro-dean for teaching and science of the Medical Faculty in Tuzla (Box 1, Figure 1).

The first generation of post-graduates were mainly employees of the Medical Faculty and the Clinical Centre in Tuzla, but also from other medical institutions in Tuzla, whilst only a few of them were from other cities. Later, the number of post-graduates from other, mainly neighbouring towns, increased from year to year. By 1986 the course had been attended by five generations of students, that is, 141 graduates, of which 57 attained their MSc degree. With the launch of this course, international cooperation began between the newly founded Medical Faculty in Tuzla, and in a relatively short period of

Figure 1 Prof. dr. Rajko Igić.

Box 1
Biography of Prof. Dr. Rajko Igić

Rajko Igić was born in Despotovo, Serbia, 1937. He attended High School (Gymnasium) in Sombor. He received his MD degree in Belgrade, his MSc in pharmacology and PhD from the Medical Faculty of the University of Sarajevo, Bosnia and Herzegovina (BH). He spent two years at the University of Oklahoma in Oklahoma City, as a Fulbright Exchange Visitor. His adviser was Dr. Ervin Erdos. Dr. Igić worked for two years as a physician in Sombor and became a research assistant, then assistant professor at the medical faculty in Sarajevo. In 1978 Professor Igić founded the Department of Pharmacology at the Medical Faculty in Tuzla and served as chairman there, and he served as chairman of the Postgraduate Studies. Dr. Igić was a Visiting Professor at the Medical Faculty in Banja Luka. He initiated and led the campain of Yugoslav medical students, *A Day Without Smoking – January 31st* that has now become the National Day Without Smoking. Dr. Igić was a recipient of the Veselin Masleša Award, and he received the Yu-Humanist Award from Croatia. The Parliament of the BH elected him in 1991 as director of the Department for Scientific Exchanges. Dr. Igić was editor-in-chief of the *Acta Medica Saliniana, Kontakt* (Contact), and *Scripta Medica.* He has published several textbooks and a large number of research papers. He is a member of the Academy of Sciences and Arts of the Republika Srpska. He now lives in Chicago, where he worked as a Senior Scientist at the Stroger Hospital of Cook County.

time rose to an enviable level. For the PS, cooperation with the Medical Faculty in Segedin (Hungary) and the Medical Faculty of the University of Shinsu, Matsumato, Japan was particularly important (4, 5). In the opinion of most of the post-graduate students of all generation from that period, the launch of the PS meant the refreshment of the medical academic community in Tuzla, refreshment, which in medical circles changed the previous way of thinking and attitude towards scientific research work.

How were the classes organized?

The classes in the PS course were held on Fridays and Saturdays. The lectures were interactive and were interesting and up to date, with the emphasis on acquiring knowledge and skills in scientific research and publication. In addition, most of the graduates had a responsible attitude towards meeting their study obligations, which was primarily reflected in their interest in active participation in acquiring new knowledge.

Some of the teaching took place at the Medical Faculty in Segedin, with which cooperation was established from the very beginning of the course, on the basis of an international agreement between the University in Tuzla and the Medical Faculty in Segedin (Hungary), signed by their rectors (4). These were compulsory scientific-professional trips for the post-graduate students, to visit the institutes and clinics of the Medical Faculty in Segedin, lasting seven days. All the classes there were held in English, in the form of lectures, demonstrations and work at individual institutes and clinics of the Medical Faculty in Segedin. Those who participated in these trips showed great interest during the classes, and the lecturers were eminent teachers from the Medical Faculty in Segedin, who were prepared to pass on their rich experience to the graduate students, in the field of scientific research work. In addition, the close and friendly relationship between the teachers from Segedin and the graduates from Tuzla made it possible to establish new forms of cooperation, which resulted in the fact that many teachers from Segedin gave lectures in Tuzla and acted as tutors for the MSc theses of our students.

Who taught the Postgraduate studies course?

Alongside the teachers from the University in Tuzla, courses in the PS at the Medical Faculty in Tuzla were also given by teachers from the Universities of Sarajevo, Belgrade, Zagreb, Ljubljana, Novi Sad, Banja Luka and Split. The teaching staff at the Military Medical Academy and the Military Technical Institute in Belgrade gave lectures on research in toxicology and held classes (for all generations) in the subjects of Medical Science and Civil Defence. At that time, teaching staff from abroad came from the USA, Japan, Germany, England, Hungary, Denmark and Sweden (6). The greatest number of teaching staff from cities in the former Yugoslavia came from Belgrade and Zagreb - a total of eighty-five, then from Sarajevo (18), Ljubljana (9), Novi Sad (5), Skopje (2), from Split and Banja Luka one each, and from other countries of that time there was a total of 29 lecturers (6). The best known among them was Ulf Svante von Euler, a Nobel Prize winner from Sweden (Figure 2) (7). Immediately before he came to Tuzla in 1982 a brochure was published entitled "Lecturers in the Post-graduate Course: Ulf Svante von Euler" (Figure 3).

What texts were used for teaching?

The textbook for the main subject, Cell Biology, of the PS of the Medical Faculty in Tuzla was the book: *Cell and Molecular Biology*, by de Robertis. As well as the Medical Facul-

Figure 2 Nobel Laureate, Ulf Svante von Euler.

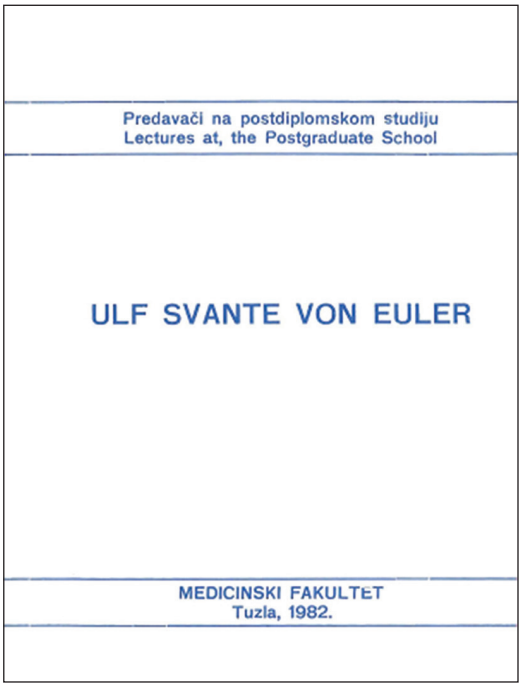

Figure 3 Cover sheet of brochures printed on the occasion of the arrival of Nobel Laureate Ulf Svante von Euler on a visit to the Medical Faculty of the University of Tuzla.

ty library, most post-graduate students also purchased this book, so tens of copies of this excellent textbook made their way to Tuzla at that time. This subject was run by the academician Mihovil Proštenik (biochemist expert in cell membranes, from Zagreb), Prof. Dr. Abdulah Nakaš and Prof. Dr. Asim Jamakosmanović (physiologists from Sarajevo), Prof. Dr. Biljana Plavšić (biologist, an expert in the electronic microscope from Sarajevo) and Prof. Dr. Ljubomir Berberović (biologist and geneticist from Sarajevo). The following books were recommended for the subject "General Methodology of Scientific Research Work and Medical Writing": *Kako nastaje naučno djelo* (How to Write a Scientific Study) by academician Midhat Šamić from Sarajevo, *Kako sastaviti, objaviti i ocijeniti znanstveno djelo* (How to draw up, publish and assess a scientific study) by academician Vlatko Silobrčić from Zagreb, and *Uvod u medicinska istraživanja* (Introduction to Medical Research) by Prof. Dr. Milorad Miro Mimica from Zagreb. Statistics were studied from the textbook *Osnovne statističke metode za nematematičare* (Basic Statistical Methods for Nonmathematicians) by Prof. Dr. Boris Petz from Zagreb and the book *Mathematics and statistics for use in pharmacy, biology, and chemistry* by Saunders &Fleming, and knowledge of scientific information was obtained from the textbook *Znanstvene informacije* (Scientific Information) by Prof. Dr. Helena Pavić from Zagreb.

Alongside the recommended literature that existed on scientific research work, for the first generation of post-graduate students, Prof. Dr. Rajko Igić issued script notes entitled *Kako se pišu saopštenja o medicinskim istraživanjima* (How to write reports in Medical Research) with a print run of 100 copies. Due to the great interest in that text shown by post-graduate students, not only at the Medical Faculty in Tuzla but also at other medical faculties in the former Yugo-

slavia, the publisher Veselin Masleša from Sarajevo published the text in the form of a book, with a print run of 1000 copies. That book was also recommended for other post-graduate courses at Medical Faculties in the former Yugoslavia. At that time it was the first book of its kind in our language, dealing with the issues involved in publishing scientific and scholarly medical texts. Later the book was cited many times in similar publications written in the former Yugoslavia. The same author also wrote brochures for the post-graduate course entitled: *Planiranje eksperimenta u kliničkim istraživanjima* (Planning experiments in clinical research) (1981), *Osnovi planiranja i statističke evaluacije bioloških, farmakoloških i kliničkih istraživanja* (The bases of planning and statistical evaluation of biological, pharmacological and clinical research) (1985) and *Uputstva za pisanje doktorske dizertacije i magistarskog rada* (Instructions for writing PhD dissertations and MSc theses) (1991), which alongside the recommended books, were the relevant textbook literature. As well as these textbooks, the teaching materials frequently used, both in classes and out of them, also included a series of publications from the index bases *Current Contents, Index Medicus,* Excerpta Medica, and tens of bio-medical journals from abroad, and many MSc and PhD papers by doctors from Tuzla and other cities of the former Yugoslavia.

Was the intended aim achieved, and to what extent?

The post-graduate course at the Medical Faculty in Tuzla was founded with the aim of preparing and training post-graduate students (future staff of the Medical Faculty in Tuzla) for scientific research work in the field of pre-clinical and clinical disciplines. The original idea to send each year 2 to 3 doctors from Tuzla for post-graduate studies to Sarajevo, Belgrade, Zagreb or some other centres of the former Yugoslavia, in order to train them for scientific research work, was unacceptable for Professor Rajko Igić. As a result he initiated the foundation of the post-graduate course at the Medical Faculty in Tuzla, with the explanation that it was better and more effective for experienced professors to come to Tuzla from other centres, than to send a small number of doctors to study at other centres. His idea was accepted and very quickly completely realized, thanks to the understanding of those responsible for the development of the faculty, primarily the dean, Prof. Dr. Ibro Pašić and the president of the Executive Board of the Municipality of Tuzla, Mr. Ljubimir Jurak.

In order to evaluate the success of the foundation and work of the PS course at the newly opened Medical Faculty in Tuzla, it was necessary to reply to the question whether and how far the intended aim had been realized. In order to answer that question I verified the number of publications before and after the graduation of the first five generations of post-graduates, because publication is necessary for further progress in an academic career, and how far the MSc graduates in biomedical sciences of those generations contributed to resolving the problem of the lack of staff at the Medical Faculty in Tuzla.

Using the key words of the surnames and initial of the 57 MSc graduates who were post-graduate students in the first five generations of the PS, I searched the number of articles they had published, before and after graduation, in journals indexed in PubMed/MEDLINE up to 2014. Before they completed their MSc, 14 articles were published, and afterwards 821 (Figure 4).

Data for this survey were collected from PubMed/MEDLINE using the keywords Bosnia and Herzegovina and 2014.

Most of those who received their MSc degree, 35 of them, later received a PhD

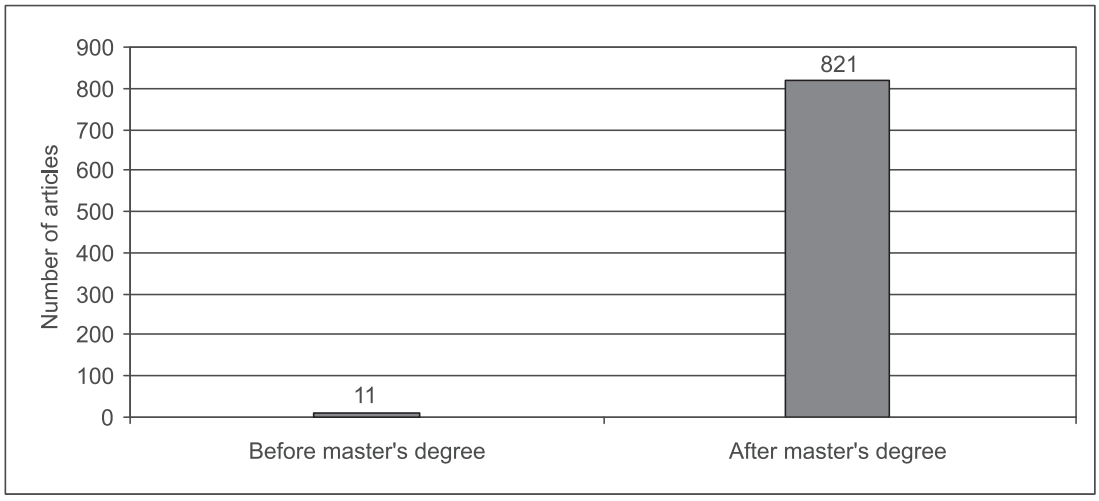

Figure 4 The number of articles before and after Master's degree of 57 graduate students published in journals indexed in PubMed/MEDLINE.

from the Medical Faculty in Tuzla or another Medical Faculty and were promoted to the position of assistant professor, and later extraordinary and regular professors, which was a significant contribution to resolving the problem of the lack of staff, but also to improving the professional and scientific work of the Medical Faculty and the University Clinical Centre in Tuzla. Some of the MSc graduates from this post-graduate course continued their careers abroad after the war broke out in 1992 and, in both a professional and a scientific sense, achieved excellent results. The author of this article and Prof. Dr. Mirsada Hukić were post-graduates in those generations, and later they were appointed members of the Academy of Sciences and Arts of Bosnia and Herzegovina.

Prof. Dr. Miralem Pašić, a graudate from this course who continued his career abroad and who in a professional and scientific sense has achieved excellent results, recently wrote this to the author of this article: "Seen from a distance of 35 years, I still believe today that the Post-graduate course of Professor Igić was one of the key pioneering moves in medicine in Tuzla. For us, the post-graduate students, Prof. Igić opened up new perspectives in our lives and science, introducing us to the world of scientific research work. He guided us to think scientifically, to observe and analyse both patients and illness, but also the world and the environment. I am extremely grateful to Prof. Igić for his visionary ideas and the work he did in our town."

Conclusion

The development of post -graduate course presented in this paper enlightened the basis for the formation and continuation of scientific as well as educative work of the Medical Faculty in Tuzla, which effects have been felt over a much wider area. Therefore this paper, based both documents and personal experience, elucidates important segment of formative period of academic development in Tuzla.

Conflict of interest: The author declares that he has no conflict of interest.

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Commentary

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Cross-cultural common denominators of the mentoring in biomedicine

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In his „ecological model of mentoring" Dr Sambunjak (1) covered all aspects of wider environmental influences on mentoring. I would like just to emphasize some of his points, which I believe are present in all environments in which a young scientist strives to do the research required for the PhD thesis. I have experienced them with a number of doctoral fellows, including the author himself (2).

1. PhD candidate should know that a decent **thesis cannot be done without "blood, sweat and tears"**. Hard work. Many years. Lots of failures and disappointments. However, science is not like football, where one can lose a well-played match because the goalkeeper had two last-minute mistakes; in science failures do not count, only successes.

2. **The doctorate is not homework**, but a pathway to becoming a scholar, someone who has gained master skills in a certain field. PhD training is aimed at young people who have chosen to do research throughout their careers, regardless of the field of medicine in which they will work.

3. **"Enlightened routine"** is a slogan which emphasizes that the PhD-related research should be done at the very workplace at which the student is employed. Working "overtime" in another institution for the PhD thesis is a wrong decision, for organizational reasons and reason given in the previous paragraph. Enlightened routine means that a part of routine, everyday work should be "wrapped" into a hypothesis and investigated thoroughly, as it should be done in good research project (3).

4. **Plan of the research** must be meticulously prepared, starting with the hypothesis, type of study, the sample, outcome measures, and other, all to the list of the potential authors of the research report and their envisioned contributions (4).

5. **Rush slowly** – acting zealously implies more intensive work, which is fine, but good research needs perfect planning, preliminary experiments, technical perfection, preparing carefully day before experiment or procedure scheduled tomorrow, discussions, and other sophisticated skills; so, one has to – rush slowly, carefully; see also No. 2 above.

6. The mentor should be the best mentor for the thesis. There are many potential

mentors around, but few are suitable because inadequate mentors prevail. Fortunately, today all data are on the internet; if the mentor has not published well, and especially if unproductive in recent times, he should be avoided: **if the mentor does not publish, there is high chance that the PhD student will not, either**.

7. Medical schools should improve their PhD programs and overall research-promoting efforts by **introducing into their obligatory graduate curricula the evidence-based medicine** (EBM) concept and work (5). EBM requires good understanding of scientific principles and technology of reasoning, criteria of excellence and critical thinking, and makes literature reading more easy, selective and critical. Using the EBM approach, School of Medicine in Split has increased its graduation rate of one reformed doctoral program to around 60% (Sapunar D, personal communication, 2015).

Conflict of interest: The author declares that he has acted as a mentor and close collaborator of Dr Dario Sambunjak.

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Commentary

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Mentoring in academic medicine: A challenging yet rewarding endeavour

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Professional advancement in academic medicine requires development of appropriate abilities for addressing complex and evolving demands of health care delivery and multifaceted service provision in order to improve populations' health. From this point of view, development and acquisition of new and appropriate skills and competencies in academic medicine should be supported by adequately tailored educational programs including mentoring functions as a basic prerequisite for personal growth and professional development.

Based on these considerations, mentoring has been also introduced in academic medicine in order to close the gap between the educational content and the competencies required in practice (1). However, little is currently known about the most effective approaches to mentoring in academic medicine. Mentoring in academic medicine is generally organized around competencies, or predefined abilities, as expected outcomes to increase performance, context-bound productivity and to improve the quality of work in clinical practice and other research and academic tasks (1). In academic medicine, however, mentoring is particularly challenging given the nature and characteristics of the profession.

Current frameworks of mentoring functions have mainly focused on individual factors including *intrapersonal* characteristics of both mentors and mentees, or *interpersonal* factors such as mentor-mentee relationships (2). On the other hand, there have been only sparse attempts to properly and comprehensively address *external* factors which may strongly influence the quality of mentoring relationships. This is mainly due to the scarcity of theoretical models underlying and guiding proper research work consisting of a holistic approach which may help to understand and appreciate the complexity of influences on mentoring, especially the quality of mentoring relationships in academic medicine, an area which includes not only teaching and research activities like the other higher education areas, but also

health care provision to individual patients and the overall population.

In order to fill this void, the article by Dario Sambunjak seeks to establish an all-inclusive conceptual framework of mentoring in academic medicine which incorporates factors operating at individual level (*micro* level), institutional level (*meso* level) and societal level (*macro* level) (3). The main contribution of Sambunjak's work relates to the explicit formulation of external factors including the *institutional* and *societal* context of mentoring in academic medicine. Future research should adequately operationalize all these factors and, subsequently, test empirically the overall model in different settings, institutional environments and different cultures (3).

Currently, the evidence on the relationship between mentorship and career choice, career progression, and scholarly productivity in countries of the Western Balkans including Albania is scarce. Particularly, research work in the field of academic medicine is quite obsolete and limited in post-communist Albania. This is mainly due to the lack of research funds, but also as a consequence of training deficits of researchers and academicians to conduct sound research in line with current international standards and best practices. In this context, mentoring related to research work would be particularly valuable for Albania and other transitional countries in the Western Balkans which face similar difficulties and challenges in the field of academic medicine. In these countries, mentoring would enable mentees access to relevant and precious resources which are basic prerequisites for successful applications and grant generation (4). Ultimately, this will enhance productivity of mentees by increasing their performance in general and the quality of research activities in particular. Nevertheless, the effectiveness of mentoring on research productivity, including publication and grant success needs to be formally assessed in countries of South Eastern Europe, as most of the research work on this topic has been conducted predominantly in Western societies (4).

In conclusion, the newly suggested ecological framework by Dario Sambunjak (3) should inform future research especially in transitional countries of South Eastern Europe – a particularly under-researched region to date – addressing adequately the individual, institutional and societal factors related to mentoring in academic medicine.

Conflict of interest: The author declares that he has no conflict of interest.

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Commentary

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Mentoring – hard and underappreciated but rewarding

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Merriam-Webster (1) defines "mentor" as one who teaches or gives help and advice to a less experienced, often younger, person. Another meaning is a trusted counselor or guide. The word originates from the name of Odysseus's friend entrusted with the education of his son Telemachus.

Mentoring is important and practically necessary in the formation of the next generation of scientists, medical doctors and other professionals, whose training requires enormous personal and societal investments. Good mentoring makes those investments hugely more productive, while lack of mentoring wastes the most important resource in our modern economy – human capital.

Thus it is important to understand what influences development of mentorship and how to incentivize and support it. In *Understanding wider environmental influences on mentoring: Towards an ecological model of mentoring in academic medicine*, Dr. Dario Sambunjak outlines "external" – societal and institutional – factors which influence mentoring in academic medicine today (2). As Dr. Sambunjak notes, some external factors are more easily influenced then others. Cultural factors are likely the most powerful influence on development of mentoring relationships, but are the hardest to influence.

Government policies are perhaps the easiest to change, but their effects often don't produce the desired results. For example, government stipends for research fellows facilitate development of mentorship, but usually lack the necessary feedback to ensure these relationships are productive and not plagued by political favoritism. Perhaps the best way governmental policies can influence mentoring is by enforcing strict scientific and ethical criteria for support of scientists. With an insistence on integrity and quality in government-supported research, the best potential mentors will be recognized and sought out by young researchers. The difficulty here is that objective criteria for quality and integrity remove the power to dispense resources (favors) from officials, which is a very difficult request to make from any government.

Perhaps the most effective way to support mentoring is at the institutional and departmental level. "Soft" approaches may

be the most effective – a department head, who personally mentors junior scientists provides a role model and influences other members of her department to do the same.

Finally, modern psychological research has revealed that humans have evolved as social beings whose happiness derives not from our status or wealth, but from fulfillment of our need for personal relationships (3). An increased emphasis on these findings as a part of general professional education may help motivate accomplished scientists, medical doctors and other professionals to take on the demanding, necessary, and rewarding task of mentoring the next generation of scientists.

Conflict of interest: The author declares that she has no conflict of interest.

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Commentary

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When to start with science teaching in academic medicine?

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Key words: Mentoring ▪ Science teaching ▪ Academic medicine

In academic medicine, mentoring was recognized to have an important influence on personal development, career choice and navigation, and research productivity (1). For this purpose, it is essential to have mentoring of high quality during the entire process of scientific research and academic degrees achievement (2). Sambunjak's article offers a holistic view of mentoring in academic medicine that may help one comprehend and appreciate the complexity of influences on mentoring, and inform the future research agenda on this important topic (2). Presented model needs to be recognized and known internationally.

The Joint Declaration of the European Ministers of Education in 1999, defined in the Bologna, needs to reshape the future of academic medicine in Europe, related to the ongoing restructuring and harmonization of a higher education (3). Bosnia and Herzegovina has the additional heavy burden of immense war destruction and population migration, which also affected medical education (3-6). In such ambient even medical students are prone to academic cheating (7).

Despite strategies proposed to alleviate the problems, research in most small and developing countries lags behind the countries belonging to the so-called mainstream science (8). According to Zerem (9) "the root of the problem in Bosnian academia – the lack of internationally recognized criteria in the acquisition of academic titles – is rarely discussed. The growing number of Masters Degrees, PhDs, and other academic titles does not reflect the reality of the scientific community. Absurdly, there is a huge number of scientists, but poor scientific production" (9).

Obligatory science teaching in medical schools in Bosnia and Herzegovina could help in building of better perspectives of academic medicine. Indeed, the group of enthusiasts, over the last 20 years, through their work as educators and editors of general medical journals dedicated to publishing research from small scientific communities has recognized that researchers from developing countries often lacked adequate training in critical assessment, research methodology and statistics. To address these prob-

lems in their own country and prevent them at their core they introduced an obligatory science teaching in medical schools in Croatia. The scientific evaluation of their course showed that they successfully satisfied 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" (8).

Conflict of interest: The author declares that he has no conflict of interest.

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Commentary

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Overcoming the impeding influences of institutional and social factors in the mentoring process

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Key words: Mentoring ▪ Personal factor ▪ Individuality

Having a mentor is critical to having a successful career in academic medicine and requires a diligent work in finding the appropriate mentor (1), but I would add that a certain amount of luck is needed as well, as that decission will certainly affect the success of a longtime work and the future of the mentee. In my case, the decission was stronlgy influenced by my mentor's previous work experience, work design and the quality of our relationship.

Mentoring style and the simplicity in communication, matching visions and expectations, with all elements of good mentoring such as role modelling, guidance and advising (both on the resarch and on my personal growth and development), together with respect of the hierarchical nature of the mentor-mentee relationship marked the course of our mentoring process.

Therefore, despite the fact that mentoring is not isolated from the outside world and social and institutional factors have different levels of interference in the process (2), I have found the personal factor to be crucial for the success of our mentoring relationship. Besides, it helped us overcome the influences of the institutional and social factors as well.

As for the institutional level, my disertation was based on the Cochrane reviews and despite the assertive view of Cochrane reviews as original research and their official acceptance as a PhD thesis, during my mentoring process, my mentor and I encountered obstacles from colleagues in terms of missunderstanding of the value of such type of research. This in turn prolonged, but fortunately did not affect the final result of our mentoring process. Active engagement by the heads of our doctoral study, their exceptional work and efforts, regular advice, and great communication were of great help and are hugely responsible for the success of our mentoring process.

Additionally, as a full time clinician it was sometimes difficult to combine my clinical work and the everyday needs and expectations of my patients with teaching and reasearch. Good relationship with my mentor together with regular support from

the heads of the doctoral study have helped me deal with that.

In the context of social levels of interference in the mentoring process, the mentor's encouragement of my individuality and my ability to take 'the driver's seat', as nicely said in the Canadian study (3), with constant supervision and help made me learn a lot and manage competently our research with all its components.

A mentor's uncompromising attitude towards reasearch integrity and fair conduct of the research process are, in addition to other things which I have benfited from in this relationship, an extremly valuable foundation for my future.

Conflict of interest: The author of the comment was a mentee of the author of the article.

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Paper review

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Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: Treating cancer like an infectious disease

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Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: Treating cancer like an infectious disease

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Authors of the study, British and American oncologists propose new strategy in the treatment of various stages of carcinomas, as well as their advanced metastases. According to them, this can be achieved via the selective targeting of cancer stem cells (CSCs), also known as tumor initiating cells.

The study can be devided into three separate parts: (1) starting point of the authors; (2) what the authors have found, and (3) what the authors propose.

1. Starting point of the authors. The starting point of the authors was based on the „endosymbiotic theory of mitochondrial evolution", since „mitochondria evolved from bacteria that were originally engulfed by eukariotic cells milions years ago". Therefore, they have common ribosomes responsible for protein biogenesis. In other words, this theory is based on global phenotipic characteristics that were highly conserved among cancer stem cells, across multiple

tumor types, i.e. in finding an Achilles' heel in cancer stem cells for the clonal expansion and their survival.

Several classes of antibiotics inhibit mitochondrial biogenesis as a known „side-effect" which, according to the authors of this study, can now be transformed into a „therapeutic effect". This will be independent of cancer type, as well as of mutated, previously resistant cells to anticancer drugs. Accordingly, the assumption of the authors was that antibiotics in this case would act on cancer as a unique disease, since the survival and growth of its cells depend only on enhanced protein biosynthesis in mitochondria.

2. What the athors have found. Studies were performed *in vitro* on the cells of eigth types of carcinoma: brain (glioblastoma), breast, DCIS (ductal carcinoma *in situ*), lung, melanoma, ovarian, pancreatic and prostate. Used antibiotics were: azithromicyn, chloramphenicol, doxycycline, tigecycline and anti-parasytic drug pyrvinium pamoate. Antibiotics were very efficient in growth inhibiton of all eight types of carcinoma. Effective concentrations of antibiotics were in micromolar range (from 1 to 250, mostly in 50 μM) and those of pyrvinium pampate in nanomolar range (250-500 nM). It has also been found that azithromycine, doxycycline, tigecycline and pirvinium pamoate were highly efficient in growth inhibiton of mutated human melanoma cells A375, which were previously resistant to vemuferanib (V600E). According to the authors, this finding proofs that the used antibiotics act on the cancer stem cells, independently of the type of cancer from which they emerge, as well as on previously mutated cells.

3. What the authors propose. The authors propose to treat cancer now like an infectious disease, by redirecting FDA-approved antibiotics for anti-cancer therapy, across multiple tumor types. These drugs are non-toxic for normal human cells, avoiding thus the numerous side effects of current anti-cancer medication. In this regard, a clinical trial with doxycycline in patients with advanced breast cancer and bone metastasis is already ongonig (https://clinicaltrials.gov/ct2/show/NCT01847976). Secondly, doxycycline trial in relapsed patients with non-hodgkin's lymphoma has also been initiated (https://clinicaltrials.gov/ct2/show/NCTo2086591).

In any case, the study is not only of highly fundamental, but could also be of much more practical importance. Namely, if the idea of the authors is confirmed, it will enable the treatment of cancer more effective, much better tolerated and manifold cheaper, making thus discovery at least equal to that of antibiotics themselves.

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by Nerma Tanović

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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).

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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.

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

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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.

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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.

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

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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.

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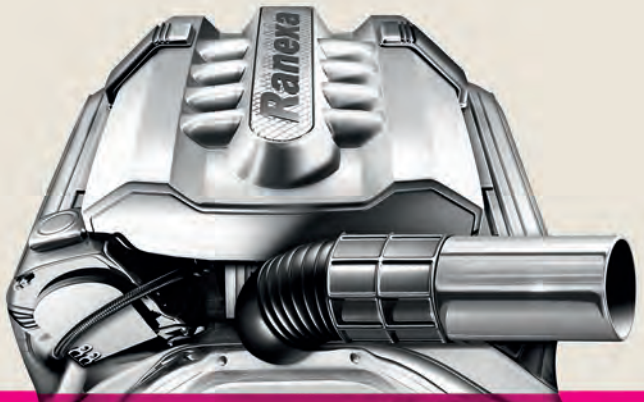

Više kisika[2]

Više snage[1]

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Za bolesnike koji boluju od stabilne angine pektoris[3]

1) Hasenfuss G et al., Clin Res Cardiol 2008; 97:222-6 **2)** Stone PH et al., J Am Coll Cardiol 2010; 56:934-42 **3)** Maier LS, Cardiovasc Pharmacol 2009; 54: 279–286

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