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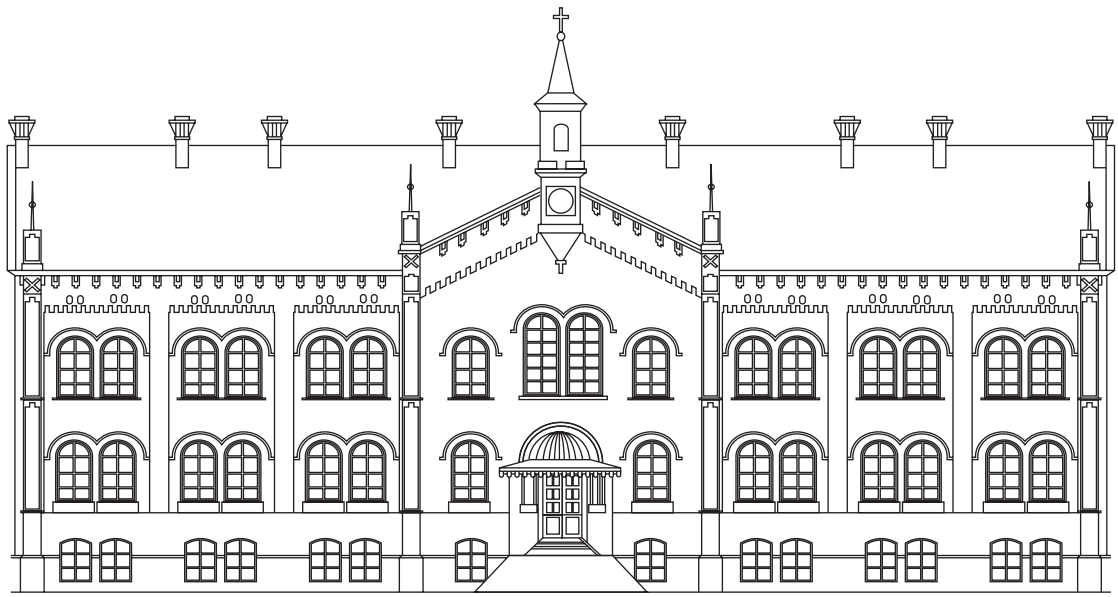

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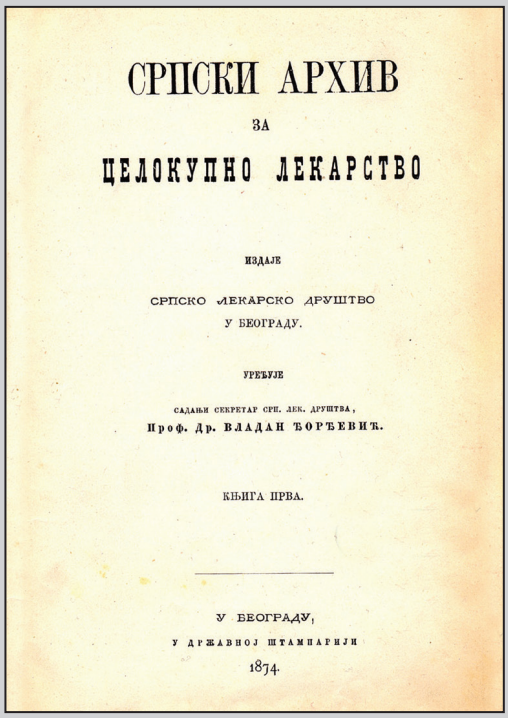

СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

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1874.

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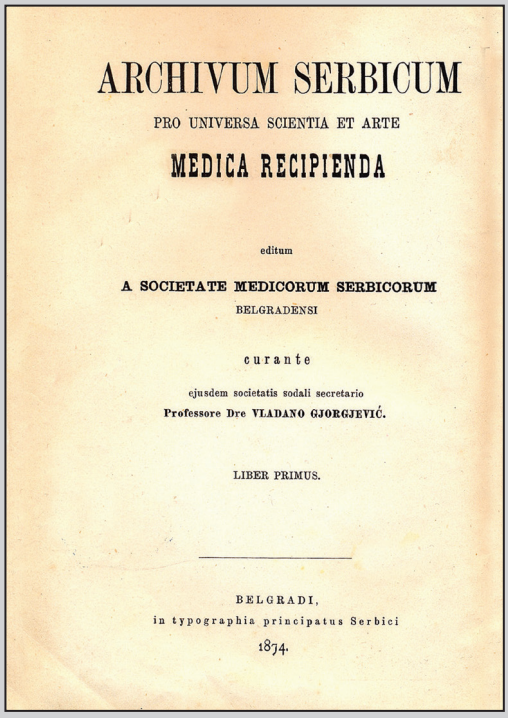

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Biomechanical behavior of periodontally compromised dento-alveolar complex before and after regenerative therapy – a proof of concept

Nataša Nikolić-Jakoba[1], Milena Barać[1], Ksenija Zelić[2], Arso Vukićević[3,4], Gordana Jovičić[3], Nenad Filipović[3,4], Marija Đurić[2]

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SUMMARY

Introduction/Objective Finite element analysis (FEA) is mathematical method which can be used for the assessment of biomechanical behavior of dento-alveolar complex.
The objectives were to analyze biomechanical behavior changes of teeth and supporting tissues under occlusal load in cases of horizontal and vertical alveolar bone loss, to assess potential impact of tooth displacement and altered stress distribution on further damage, and to evaluate the impact of regenerative periodontal therapy.

Methods Three patient-specific three-dimensional finite element (3D FE) models were developed from the acquired cone beam computed tomography, comprising the patient's upper left canine, first and second premolar, and adjacent bone. Model 1 represented horizontal bone loss. Model 2 included intrabony defect along distal aspect of tooth #24. Model 3 represented situation six months after the regenerative periodontal surgery. Displacement, Von Mises, and principal stresses were evaluated through FEA, under moderate vertical occlusal load.

Results FEA demonstrated that in the model with vertical bone loss significant tooth displacement was present, even though the clinically evident tooth mobility was absent. Biomechanical behavior and stress distribution of teeth and surrounding tissues under moderate occlusal load was much more altered in case with vertical bone loss in comparison with horizontal bone loss. Six months following the regenerative therapy, the values of all evaluated parameters were noticeable reduced.

Conclusion Regenerative periodontal therapy improved the biomechanical characteristics of the affected teeth and the related periodontal structures.

Keywords: periodontal disease; alveolar bone loss; guided tissue regeneration; finite element analysis

INTRODUCTION

Alveolar bone loss is one of the main features of periodontitis. Bone defects may vary in their localization, shape, and extent. Generally, bone destruction may occur in two diverse patterns, as horizontal or vertical bone loss [1]. Horizontal bone loss is the most commonly seen and it is characterized by the linear reduction of bone height around the tooth. The vertical or angular bone defects are those that appear in the oblique direction [1]. Deep vertical (intrabony) defects associated with vertical bone loss are the standard indication for periodontal regenerative therapy [2].

It is evident that tooth with reduced bone support has compromised occlusal force transition to the jaws, and the further damage the residual periodontal tissues may occur [3]. In cases of horizontal or vertical bone loss different stress distribution may be expected. However, what is the outcome of these differences and how much do they affect the tooth? Would the increased stress level further harm the remaining periodontal tissues? How high is the level of stress in the affected supporting tissues if the tooth does not have clinically evident pathological mobility? There is not enough scientific evidence which could give the answers to these questions.

Several regenerative procedures aiming at repairing the lost periodontal tissues, including the alveolar bone, periodontal ligament (PDL), and root cementum are in daily practice [4]. Although therapy of periodontitis aims to eliminate the periodontal pockets as the main collector of subgingival deposits and microorganisms, we are questioning the influence of the regenerative periodontal therapy on biomechanical behavior of affected dento-alveolar complex. Literature survey demonstrated that the biomechanical aspect of differences between horizontal and vertical bone loss cases has not been analyzed and fully understood so far. Furthermore, benefit in biomechanical behavior after surgical regenerative treatment has not been analyzed. Moreover, it has already been pointed out that clinically evident tooth mobility negatively

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influences the outcome of the regenerative therapy [4]. However, is it also important to analyze the biomechanical behavior of teeth and related structures in periodontally affected sites without measurable tooth mobility?

Three-dimensional finite element (3D FE) method is a very powerful tool which can give insight into the biomechanical behavior of analyzed dento-alveolar complex. It has been widely implemented in research related to dentistry [5–13].

In this study, the first objective was to analyze the stress distribution in cases with horizontal and vertical bone loss with no clinically evident tooth mobility. The goal was to test the hypothesis that in case of vertical bone loss PDL and alveolar bone are affected with higher occlusal stress which could further damage these structures, despite the fact that tooth mobility was not detected. The second aim of the study was to investigate whether regenerative periodontal therapy decreases displacement and stress values in the affected teeth and surrounding tissues. We used 3D FE analysis of three patient specific models developed from cone beam computed tomography (CBCT) in order to mimic the clinical situations.

METHODS

A CBCT image of a 38-year-old man was used to create a patient specific 3D FE models. The patient was in good systemic health, nonsmoker, with generalized severe chronic periodontitis. The patient was thoroughly informed about the purpose of the study and gave his written consent before clinical examination. The study was approved by the Ethics Research Committee of the School of Dental Medicine, University of Belgrade, Serbia (ethics approval Nº 36/41).

Surgical procedure

Six weeks following the initial periodontal therapy, the patient underwent a periodontal surgery for the debridement of all periodontal defects with probing depth ≥ 6 mm. Periodontal clinical parameters were assessed using a manual periodontal probe graded in millimeters (PCPUNC-15; HU-Friedy, Chicago, IL, USA): probing pocket depth (PPD), gingival recession, and clinical attachment level (CAL), whereas only the deepest site per tooth was reported (tooth #23: PPD = 3 mm, CAL = 2 mm; tooth #24: PPD = 8 mm, CAL = 8 mm; tooth #25: PPD = 4 mm, CAL = 3 mm). After application of local anesthesia, intrasulcular incisions were performed from the distal aspect of the tooth #23 to the distal aspect of the tooth #27. A full-thickness flap was reflected buccally and palatally. The denuded roots were thoroughly debrided using ultrasonic devices and hand instruments. Exposed roots were chemically prepared with 24% EDTA gel (PrefGel®, Biora, Malmö, Sweden and Straumann, Basel, Switzerland) and rinsed thoroughly with sterile saline before the application of enamel matrix derivative (EMD) (Emdogain gel®, Biora and Straumann). Subsequently, a three-wall intrabony defect along the distal aspect of tooth #24 was reconstructed using bovine porous bone mineral granules (BioOss®, particle size 0.25–1 mm; Geistlich Pharma, Wolhusen, Switzerland). Flaps were repositioned and sutured using the standard procedure. A post-operative visit was scheduled in seven days when the sutures were removed. Six months following the surgery periodontal clinical parameters were assessed (tooth #23: PPD = 3 mm, CAL = 2 mm; tooth #24: PPD = 3 mm, CAL = 4 mm; tooth #25: PPD = 3 mm, CAL = 3 mm).

Cone beam computed tomography scanning

Imaging was performed using a high resolution CBCT device (SCANORA 3Dx, SOREDEX, Tuusula, Finland). The patient was scanned twice, before periodontal surgery and six months following the surgical procedure. Examinations were performed using an 80 × 100 mm field of view, 0.25 mm voxel size, 90 kV tube voltage, and 10 mA tube current and 2.4 s scanning time. All the scans were stored in the standard DICOM format for the further analysis.

Finite element analysis

Development of the finite element models

In total, three patient-specific 3D FE models were developed from the acquired CBCT scans (Figure 1a–c). The models comprised the patient's upper left canine, first and second premolar, and adjacent alveolar bone. For each tooth, we considered its enamel, dentin, pulp chamber, and PDL, while the root cementum was neglected. Mimics software version 10 (Materialise, Leuven, Belgium) was used for the reconstruction of the FE models from the CBCT scans through the following steps. The masks of cortical, trabecular bone and teeth were generated respectively. The Mimics STL+ model was used to convert all the masks into the stereolithography (STL) format. In order to optimize the quality of the triangle meshes for the further FEA, we used the REMESH module attached to Mimics software. At last, by using Geomagic Studio 10 software (Geomagic GmbH, Stuttgart, Germany) we assembled the extracted parts into the three models. A PDL as the 200 μm-thick shell was additionally generated. Bone level adjacent to teeth #23 and #25 did not differ in all three 3D FE models. Likewise, bone level adjacent to tooth #24 was the same in Model 1 and Model 3, while the detailed description of the models is as it follows:

Model 1 represents horizontal bone loss in region #23, #24, and #25 (Figure 1a). It was constructed based on the CBCT scans of the patient's upper jaw before the surgery (Figure 1d), but with certain changes, the vertical bone defect (intrabony defect), which was localized along the distal aspect of tooth #24, was reconstructed by applying the properties of cancellous and cortical bone in order to simulate horizontal bone loss. This model was created in order to examine the differences in displacement and stress distribution between the horizontal (Model 1) and vertical (Model 2) bone loss patterns, and to compare with the

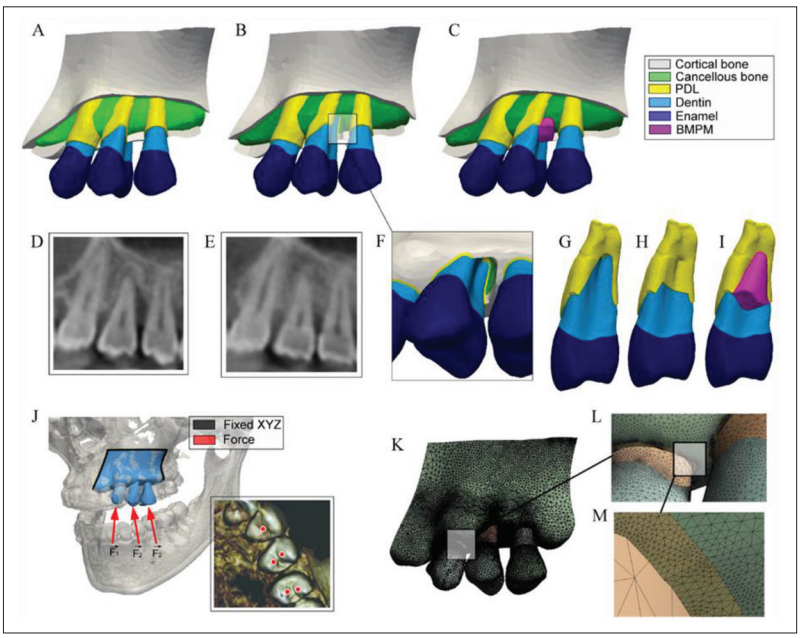

Figure 1. Overall procedure: a – model 1; b – model 2; c – model 3; d – before surgery; e – six months after surgery; f – intrabony defect; g – tooth #24 periodontal ligament (model 2); h – tooth #24 periodontal ligament (model 3); i – bovine porous bone mineral granules; j – boundary conditions and application of masticatory forces; k, l, m – tetrahedron volume mesh

Table 1. Mechanical properties of the modeled tissues and material

Material	Elastic Modulus (MPa)	Poison ratio
Pulp [9]	6.8	0.45
Dentin [6]	18.6×10^3	0.31
Enamel [6]	84.10×10^3	0.3
PDL [6, 23]	0.68	0.45
BMBP [5]	1.69×10^3	0.3
Cortical bone [15]	13.7×10^3	0.3
Cancellous bone [15]	1.37×10^3	0.3

PDL – periodontal ligament; BMBP – bovine porous bone mineral (values after six months of healing period)

situation achieved six months following the regenerative periodontal surgery (Model 3). Hence, bone level adjacent to tooth #24 was the same in Model 1 and Model 3.

Model 2 represents a patient-specific FE model, generated by using preoperative CBCT scans (Figure 1d), representing an identical situation in the region of interest before regenerative periodontal surgery (intrabony defect along the distal aspect of tooth #24 (Figure 1b, f)). PDL was not modeled on the tooth #24, at the root's site adjacent to the intrabony defect (Figure 1g).

Model 3 represents a patient-specific FE model created from CBCT scans acquired six months following the surgical procedure (Figure 1e). Reconstructed intrabony defect along the distal aspect of tooth #24 was modeled, whereas the material properties of bovine porous bone mineral granules six months following the surgical therapy was applied [5] (Figure 1c and i). Bone level adjacent to teeth #23 and #25 did not differ in all three 3D FE models.

In the region of reconstructed intrabony defect 80% of PDL was created, starting from the bottom of the defect towards the alveolar crest, based on previous histological findings when this treatment protocol was applied (Figure 1h) [14].

Meshing and material properties of the tissues

The STL files of the developed models were imported into the CATIA V5 software (Dassault Systèmes, Velizy-Villacoublay, France) version R20, and converted into the NURBS surfaces using the Digitized Shape Editor and Quick Surface Reconstruction modules. The solid models were further exported to ANSYS software (SASI, Canonsburg, PA, USA), version 14.5.7, for producing the FE mesh and structural analysis. By using the ANSYS Meshing module, the models were discretized into the very dense and quality tetrahedron volume mesh (Figure 1k-m). Number of nodes for Model 1, Model 2 and Model 3 was 1176135, 1179101, and 1228269 respectively; while the number of finite elements for the models was 5684279, 5702597, and 5952010 respectively. All the tissues were assumed to be homogeneous and linearly elastic. The values of the Young's moduli and the Poisson's ratios for dental tissues, PDL, cortical and cancellous bone, and BMBP were taken from the literature (Table 1).

Boundary conditions and calculations

In order to assess the stress distribution (Von Mises, compressive, tensile) and effective displacements, the same boundary conditions were applied on each model using the ANSYS Static Structural Analysis module (Figure 1j). The sides of models that represent cut-off planes from the overall maxilla were fixated in all degrees of freedom following Figure 1j, black color. Masticatory forces were applied on the buccal and lingual cups of premolars simultaneously (Figure 1j – red arrows, red color), to gain the resulting force of 200 N parallel to the long axis of these teeth (vertical load) [15]. Load of 150 N was applied at an angle of 45° to the center of the canine's palatal surface within the physiological limitations reported for a canine [15].

RESULTS

The results for the displacement, Von Mises and principal stresses for all three models are presented on Figures 2–5.

Results in this study showed that alveolar bone loss patterns may cause differences in the tooth displacement. Although displacement of tooth without bone resorption was not tested, it may be notice that the greatest influence had vertical bone loss before regenerative therapy and the greatest displacement of all evaluated teeth was detected in this case (Figure 2). Since the characteristics and the height of tooth supporting tissues differed only in region

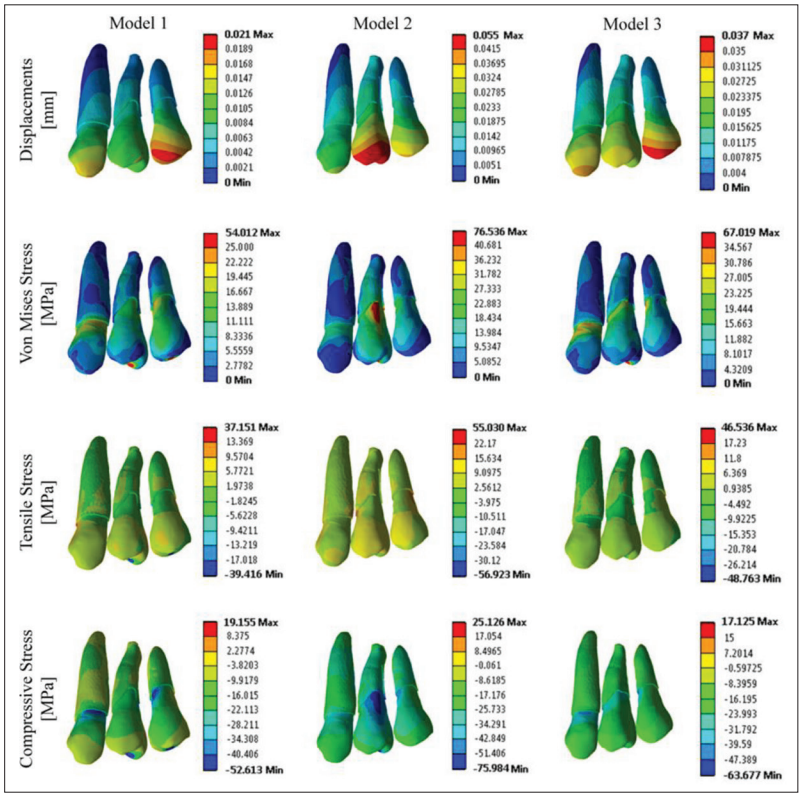

Figure 2. Displacement, Von Mises, tensile and compressive stress in the teeth and periodontal ligament in all three three-dimensional finite element models

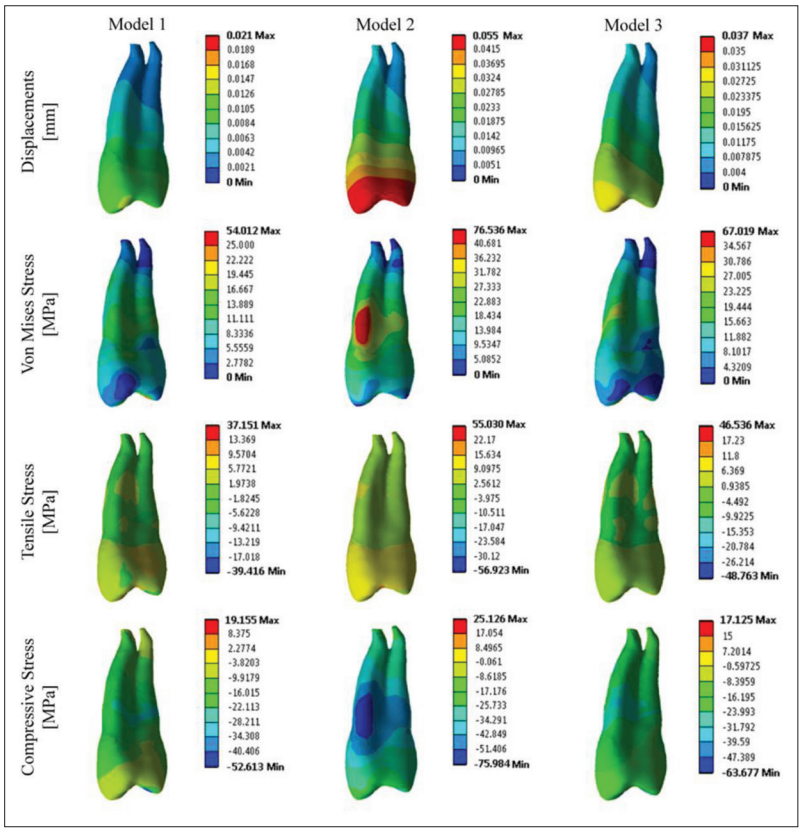

Figure 3. Displacement, Von Mises, tensile and compressive stress in the tooth #24 in all three three-dimensional finite element

of tooth #24 in all three models, this tooth exhibited the biggest differences in displacement (Figure 3). Under occlusal force, the tooth inclined toward bone defect. Displacement of tooth #24 was five times greater in case of vertical bone loss compared to horizontal bone loss. Moreover, it was noticed that tooth #25 in Model 2 also exhibited displacement towards the defect adjacent to tooth #24 (Figure 2). On the other hand, six months following the surgical treatment and bone defect reconstruction, displacement of these teeth significantly diminished, but was greater than the values which were present in case of horizontal bone loss (Model 1).

Analysis of stresses distribution in teeth showed significant differences between Model 1 and Model 2 (Figure 2). Higher values of Von Mises were seen especially in tooth #24 (Figure 3). However, six months after the surgery, the level of stresses was noticeably lower. These findings are in agreement with the results of the teeth displacement.

Assessing alveolar bone in all three 3D FE models showed that Von Mises stresses had greater magnitudes in cortical bone when compared to cancellous bone (Figures 4 and 5). In all three models, maximum stress values were present in narrow zones of alveolar crest (Figure 4). Only in the case of the vertical bone loss Von Mises stresses reached maximum values of 76.54 MPa in alveolar crest at distopalatal aspect of tooth #24. Evaluation of the buccal and palatal aspects of maxilla, demonstrated that buccal plate was affected at a higher level, and the widest stressed zone was observed in the case of vertical bone loss (Figure 4). Six months following the surgery, both buccal and palatal plates exhibited lower stresses values, and stress distribution was similar to that detected in the case of horizontal bone loss. Figure 5 displays uniform Von Mises stresses distribution in cancellous bone for all three models. Concerning the pattern of bone destruction, the highest stresses values in cancellous bone were revealed in the case of vertical bone loss. The stress was obviously reduced six months following the surgery, but did not achieve values exhibited in the case of horizontal bone loss. Analysis of the principal stresses revealed that the in Model 2 (vertical

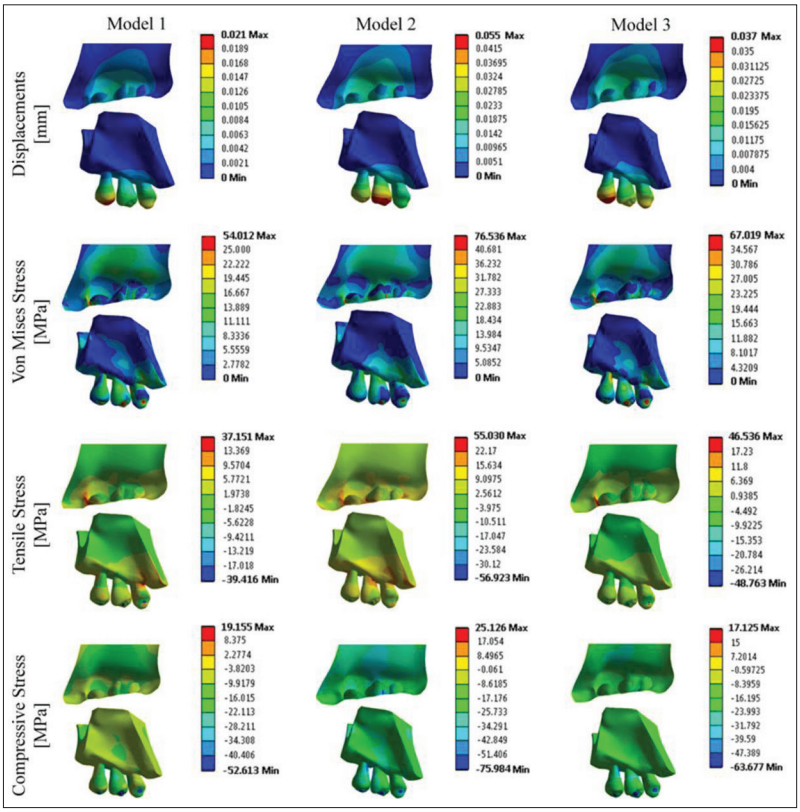

Figure 4. Displacement, Von Mises, tensile and compressive stress in cortical bone in all three three-dimensional finite element

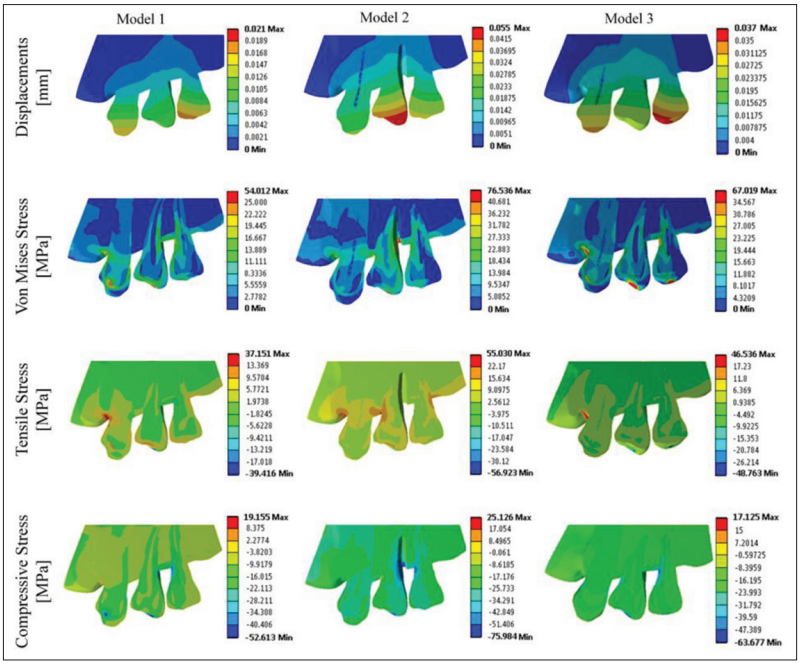

Figure 5. Displacement, Von Mises, tensile and compressive stress in cancellous bone in all three three-dimensional finite element

bone loss) tensile stresses were generated in alveolar crest at mesial aspect of the tooth #24, while the compressive stresses were noticed on the opposite (distal) aspect of the tooth. Six months after the surgery, the levels of principal stresses decreased but remained higher than in Model 1 (horizontal bone loss) (Figure 4).

Regarding the PDL, the highest Von Mises stresses was also present in the case of vertical bone loss, mostly located on the buccal and mesial aspect of the tooth #24 root (Figure 2). Six months following the surgery, the stress magnitude in PDL was obviously reduced and uniformly distributed, not only in the case of tooth #24 but in all evaluated teeth, and reached the values detected in the case of horizontal bone loss.

DISCUSSION

The present concept and use of computer modeling followed by FEA allows the insight into the stress transition of occlusal forces into the alveolar bone. In this study we were able to visualize the undetectable values of tooth displacement and to analyze its influence on stress distribution.

Results of this study supported the hypothesis that higher stresses are generated during occlusal load in teeth affected with vertical than in horizontal bone loss. Also, as it was hypothesized, regenerative periodontal therapy decreased displacement and stress values in the affected teeth and supporting periodontal structures. However, it was demonstrated that six months following the surgery the magnitude of these values were still higher than the values detected in case of horizontal bone loss, although the coronal level of bone was the same.

Jang et al. [16] using the FEA method showed that the diverse extent of periodontal bone loss had a greater impact on biomechanical response. In the present study we analyzed tooth displacement which was not clinically detected. It was demonstrated that, although being small, tooth displacement affects the level of principal stresses. Namely, tooth #24 was "bending" distally towards the intrabony defect (Model 2) (Figure 3). Subsequently, tensile stress was generated on the mesial aspect of adjacent alveolar crest, while compressive stress was developed on the distopalatal edge (Figure 4). In the case of horizontal bone loss (Model 1) our results showed much lower values of tooth displacement and principal stresses in the bone.

Even though the maximal vertical biting forces in humans can approach 700 N [17, 18], the moderate physiological occlusal forces in this study (150 N and 200 N) can cause localized stress concentrations in alveolar bone

affected by vertical resorption. It was revealed in the study of Jeon et al. [8] that localized stress concentrations are closely related with bone resorption. Knowing that yield stress of 60 MPa may cause harmful effects on cortical bone in humans [19], detected value of 75.98 MPa would have detrimental effects on cortical bone and most likely would lead to further bone resorption. Furthermore, fatigue loadings that are continuous and repetitive can potentially "accumulate" the stress, triggering bone degeneration or resorption [20]. In the study, the highest values of localized compressive stress were detected at palatal alveolar crest adjacent to intrabony defect (Figure 4), which might be an area of further bone resorption, supported by bacterial stimulation [21].

In this study, BPBM and EMD were used to promote periodontal regeneration in the treatment of periodontal disease. Histological examination in humans showed that bone defects treated with the combination EMD–BPBM healed with a new connective tissue attachment and new bone [22]. These findings were used (and applied) in this study to create PDL in the Model 3 (Figure 1h). We applied the values for mechanical properties of BPBM following the six months healing period, described in the work of Kwon et al. [5]. They demonstrated that stiffness of BPBM six months following the surgery (1.69×10^3) was slightly greater than cancellous bone (1.37×10^3). Even though the new-formed bone (six months following the surgery) was stiffer than the natural cancellous bone, FEA results showed that the displacement of the tooth #24 was still greater than in the Model 1. This is probably the consequence of the lack of cortical bone in this area, which is much stiffer. However, stress levels were significantly diminished, especially the high tensile stress in alveolar crest at the mesial aspect of this tooth. Thus, we can conclude that even though the therapy could regenerate bone to approximate level of the alveolar crest in the case of intrabony defects with favorable osseous architecture [4], this study showed that there is still the weak point at the previously affected site which is jeopardized in terms of further bone loss (Figure 4).

FE studies showed that in an area with periodontal disease bone support and PDL area are reduced, and the same magnitude of occlusal load will cause higher stress in the PDL [8, 10]. This should be bear in mind, because even the physiological occlusal loads may result in high stress values which may contribute to further bone loss. Ona et al. [3] described in their FE study that bone resorption will reduce the root area available for support, which may cause an increase of the maximum stress within the PDL. Results of our study are in agreement with this finding, as the highest value of overall stress was detected in PDL of tooth #24 in the case of vertical bone loss (Figure 2). However, this value was evidently reduced six months following the surgery since the root area available for support has been expanded.

In the present study, using CBCT scans before and after regenerative therapy was an advantage. Experimental study with the same study design would be impossible, since horizontal bone loss, vertical bone loss (intrabony defect), and reconstructed intrabony defect were simulated in the same region allowing comparison of the gained results.

It is important to emphasize that the results should be interpreted with caution due to the study's limitation. Namely, as this study is based on computer simulations, some simplifications were made. Only a nondestructive static occlusal loading was applied, and the dynamic loading behavior which is present in the oral cavity was not simulated. Furthermore, aiming to avoid the influences of load directions only the vertical occlusal forces were evaluated, while horizontal and oblique forces were neglected.

To the best of authors' knowledge, this is the first study which provided the basic information of biomechanical aspects in periodontal tissues regarding the diverse pattern of bone loss, and may serve as s basic template which could be useful for calculating the effectiveness of different approaches in regenerative periodontal treatment.

CONCLUSION

This study demonstrated that computer modeling and FEA can give new information regarding the biomechanical behavior of periodontal structures when diverse patterns of bone loss are present. Followed by CBCT, in a patient specific model, this method revealed significant displacement of periodontally compromised tooth, whereas tooth mobility was not clinically evident. The tooth displacement caused high stresses which could be potentially dangerous in promoting further bone resorption. Resolution of vertical bone defect resulted in reduction of tooth displacement and significantly lower level of principal stresses in the bone. However, the magnitude of these values was higher than the values detected in case of horizontal bone loss, showing that there is still a weak point at the previously affected site which is in jeopardy for further bone loss.

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Conflict of interest: None declared.

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Биомеханичко понашање структура денто-алвеоларног комплекса пре и после регенеративне терапије пародонтопатије

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САЖЕТАК

Увод/Циљ Метод коначних елемената је математички метод који се може користити у циљу испитивања биомеханичког понашања структура денто-алвеоларног комплекса.

Циљ овог рада је био испитати биомеханичко понашање зуба, периодонцијума и околне алвеоларне кости под дејством оклузалних сила у случају присуства различитих типова ресорпције алвеоларне кости пре и после регенеративне терапије пародонтопатије.

Метод На основу радиолошких слика добијених компјутеризованом томографијом конусног зрака креирана су три тродимензионална математичка модела која су се састојала од горњег левог очњака, првог и другог премолара и околне алвеоларне кости. На моделу 1 је представљен хоризонтални губитак алвеоларне кости. Модел 2 је садржао инфракоштани дефект дуж дисталне површине зуба #24. Модел 3 је представљао ситуацију шест месеци после регенеративне терапије пародонтопатије. Применом метода коначних елемената израчунати су степен померања зуба, интензитет и дистрибуција *Von Mises* и главних напона под дејством умерених оклузалних сила.

Резутати Метод коначних елемената је показао да у моделу са вертикалним губитком кости постоје значајна померања зуба услед дејства оклузалних сила, а самим тим и већи интензитет напона у периодонцијуму и околној алвеоларној кости у односу на хоризонтални губитак кости. Шест месеци после регенеративне терапије пародонтопатије степен померања и интензитети напона су били знатно смањени.

Закључак Регенеративна терапија пародонтопатије утиче на побољшање биомеханичких карактеристика зуба, периодонцијума и околне алвеоларне кости.

Кључне речи: пародонтопатија; ресорпција алвеоларне кости; усмерена регенерација ткива; метод коначних елемената

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Oral health of prosthetic rehabilitated patients with schizophrenia

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SUMMARY

Introduction/Objective Factors such as nature of psychiatric disorder, length of hospitalization and oral-side effects of psychotropic medications may considerably contribute to high prevalence of oral diseases among people with schizophrenia, and a consequent need for prosthetic rehabilitation. The aim of this study was to ascertain the oral health level of prosthetic rehabilitated patients with schizophrenia and to consider their needs for future improvement of prosthetic rehabilitation.

Methods The study group comprised 52 patients with schizophrenia, hospitalized at the Dr Laza Lazarević Clinic for Mental Disorders, Belgrade. The control group comprised 52 patients with no psychiatric medical history, treated at the School of Dental Medicine, University of Belgrade. The oral health indices (Decayed, Missing and Filled Teeth Index – DMFT, Community Periodontal Index of Treatment Needs – CPITN, and the Simplified Oral Hygiene Index – OHI-S), socio-demographic characteristics, smoking habits, oral hygiene habits, and previous dental visits were registered in both groups, as well as medical characteristics of the primary disease in the study group patients.

Results Fifty percent of the study group patients had partial mobile dentures, while almost 30% had fixed dentures, in contrast to the control group patients, who prevalently had fixed dentures. In both groups of patients, a statistical significance was observed between partial mobile and fixed dentures wearers, in terms of DMFT index, carious teeth, CPI modified, and OHI-S. Similarly, a statistically significant difference between the groups was observed concerning fixed dentures in terms of carious teeth, filled teeth, CPI modified, and OHI-S.

Conclusion Multidisciplinary approach is needed for complete oral and prosthetic rehabilitation of this group of psychiatric patients.

Keywords: prosthetic; schizophrenia; oral health

INTRODUCTION

Physical health of patients with schizophrenia seems to receive much attention over recent years because this group of psychiatric patients has been significantly increasing, and they are less likely to receive the level of physical-based care and rehabilitation they need [1]. Also, studies indicate that positive and negative symptoms of schizophrenia correlate with poor quality of life [2, 3]. In addition, the chronicity of the schizophrenia has been attributed to the undesirable consequences that potentially devastate oral health [4].

Oral health is an integral part of the general health. Dental caries that constitutes a significant public health problem worldwide is a common chronic infectious transmissible disease [5]. Apart from poor oral hygiene and diet (in particular, sugar-rich food), many other factors have always been associated with it [5]. Similar to that, periodontitis is microbe-induced inflammatory and multifactorial oral disease, characterized by inflammation of periodontium and loss of the periodontal attachment apparatus [6]. In addition, these changes can lead to serious consequences such as tooth loss and a lower quality of life [7].

Many studies have shown that people with schizophrenia are at an increased risk of poor oral health [8–12]. Factors such as nature of psychiatric disorder, length of hospitalization and oral side effects of psychotropic medications may considerably contribute to high prevalence of oral diseases among this group of psychiatric patients, and a consequent need for prosthetic rehabilitation [8]. However, dental treatment of people with schizophrenia is not an easy task, primarily because they avoid regular visits to dental offices due their financial situation and a neglected maintaining adequate oral hygiene [8]. Poor oral hygiene and dental neglect in this group of psychiatric patients seems to lead to pain and infection processes, negatively impacting not only physical health, but also the quality of life, social functioning, and self-esteem [9].

According to evidence that persons with schizophrenia have a higher number of dental carious and missing teeth than the general

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population, with severe form of periodontitis, poor oral hygiene, and that some of them already have some kind of prosthetic appliance, the aim of this study was to assess the oral health of patients with schizophrenia rehabilitated with prosthetics and to consider options of their needs for future improvements of prosthetic rehabilitation [8–12].

METHODS

Study population

This cross-sectional study was conducted at the Dr. Laza Lazarević Clinic for Mental Disorders, Belgrade (for the study group patients) and at the School of Dental Medicine, University of Belgrade (for the control group of patients), in full accordance with the World Medical Association Declaration of Helsinki. Also, the approval from the ethics committees of both medical institutions was received. All participants or their legal guardians (for the study group patients) were informed through a special brochure (concerning the type of the research, data collection procedure, and other aspects of the study), and they signed the informed consent form before participating in any part of the study.

The study group comprised 52 patients with schizophrenia (18 males and 34 females, aged 25–67 years; mean age 47.56 ± 10.59 years), hospitalized at the Dr Laza Lazarević Clinic for Mental Disorders, Belgrade. The inclusion criteria for entering the study group were that the patients were older than 18 years at the time of the study, diagnosed with schizophrenia in accordance with the 10th Revision of the International Classification of Diseases minimum two years prior to the study, and that they had some kind of oral prosthetic rehabilitation at the time of hospitalization. The exclusion criteria for the study group patients were the primary diagnosis of another mental disorder, hospitalized patients diagnosed with schizophrenia in the period shorter than two years from the time of the survey, patients who were not prosthetic rehabilitated before the study, the simultaneous presence of severe somatic illnesses or severe disability, and inability to communicate or the refusal to cooperate.

The control group comprised 52 patients (19 males and 33 females, aged 19–71 years; mean age 49.10 ± 10.99 years), treated at the School of Dental Medicine, University of Belgrade. They were matched to the study group by the number of participants, sex, and roughly by age. The inclusion criteria for entering the study were patients older than 18 years at the time of the study, with no medical history in terms of mental disorders, and also that they already had some kind of prosthetic rehabilitation. The exclusion criteria were the diagnosis of any psychiatric or somatic illness and the use of drugs that can cause oral changes (antibiotics, antifungals, blood pressure medication, corticosteroids, diabetes medication, etc.) [13].

A questionnaire for both groups of patients was designed in order to record the socio-demographic characteristics (gender, age, educational level, marital status, and residence), smoking habits, oral hygiene habits, and previous dental visits. The data about schizophrenia in the study group were taken from the medical records and included the duration of schizophrenia, number of previous hospitalizations, and current psychotropic medication.

Clinical examination

All the patients were subjected to the thorough dental clinical examination in accordance with the criteria recommended by the World Health Organization [14]. The dental clinical examinations were carried out by two trained and calibrated examiners at the Dr Laza Lazarević Clinic for Mental Disorders in Belgrade, Serbia, and the Faculty of Dental Medicine, University of Belgrade, Serbia, in order to assess the Decayed, Missing and Filled Teeth Index (DMFT index) [14], Community Periodontal Index (CPI) modified [14], and Oral Hygiene Index – Simplified (OHI-S) [15]. In terms of the DMFT index, the examinations were performed in the daylight, using mouth mirror [14]. In addition, clearly visible lesions with cavities on tooth surfaces were registered as caries, teeth with only a change in transparency, but with intact surface and without cavitation were registered as being healthy [14]. In terms of CPI modified, the clinical measurements were performed by using the periodontal CPI probe graded in millimeters on the sextants, scoring on the scale 0–4. In each sextant, all teeth were examined and only the highest value for each sextant was scored and recorded [14]. OHI-S was composed of two components, the Debris Index and the Calculus Index. These indexes represented the amount of debris or calculus found on the preselected surfaces of the indexed teeth [15].

Statistical analysis

All collected data were organized and evaluated using the dedicated software (SPSS Statistics, Version 17.0; SPSS Inc, Chicago, IL, USA) and were analyzed by the descriptive statistical parameters and regression models. The descriptive statistical methods were represented by the measures of central tendency (mean and median), measure of variability (standard deviation and variation interval), and were expressed in the percentages. The methods for testing the difference of numerical data (DMFT index, CPI modified, and OHI-S) were represented by the Mann–Whitney test. For testing the data of different categories (socio-demographic characteristics, smoking habits, oral hygiene habits, and previous dental visits), Person's χ^2 test was used. The level of significance was set at $p \leq 0.05$.

RESULTS

Types of prosthetic appliances in both groups of patients are shown in Figure 1. Fifty percent of the study group patients had partial mobile dentures, while almost 30% had fixed dentures (crowns and/or bridges), in contrast to the control group patients, who prevalently (76.9%) had fixed dentures – Figure 1.

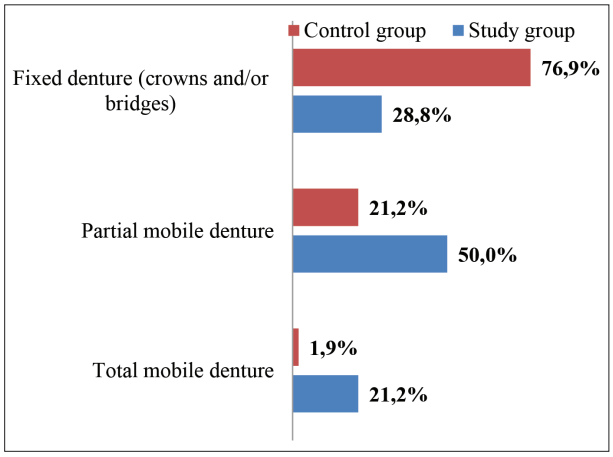

Figure 1. Types of prosthetic dentures in the study group and the control group

Table 1. Socio-demographic characteristics of the study group and the control group

Socio-demographic variables	Obtained values		Significance[a] (p)
	Study group n (%)	Control group n (%)	
Education:			
without school / elementary school	7 (13.5)	2 (3.8)	
junior high school	31 (59.6)	16 (30.8)	
high school	5 (9.6)	11 (21.2)	
university	9 (17.3)	23 (44.2)	0.001*
Employment:			
unemployed			
employed	30 (57.7)	25 (48.1)	
invalid retirement	5 (9.6)	14 (26.9)	
age or survivor retirement	7 (13.5)	2 (3.8)	
	10 (19.2)	11 (21.2)	0.056
Marital status:			
married	6 (11.5)	19 (36.5)	
divorced/separated	5 (9.6)	13 (25)	
unmarried/single	40 (76.9)	17 (32.7)	
widowed	1 (1.9)	3 (5.8)	0.000*
Residence:			
own property	18 (34.6)	26 (50)	
parents' property	25 (48.1)	13 (25)	
rent or other	9 (17.3)	13 (25)	0.005*

*statistically significant;
[a]Pearson's χ^2 test

The distribution of socio-demographic characteristics of both groups is shown in Table 1. The statistically significant differences between the groups were observed for education, marital status, and residence status (Table 1). The educational level of patients with schizophrenia was lower than that of the control group patients. Furthermore, the percentage of employees among the study group patients was significantly lower than that in the control group (Table 1). Also, most of the study group patients lived with their parents, in contrast to the control group patients, who predominantly owned their own homes (Table 1).

In the study group, schizophrenia lasted 17.79 ± 9.59 years (range 2–45 years), and the average number of hospitalizations was 9.54 ± 5.15 (range 1–25 hospitalizations) – Table 2. The patients with schizophrenia were treated with an average of 4.18 ± 1.07 psychotropic medications (range 2–7) – Table 2. Also, the average number of antipsychotics

Table 2. Medical characteristics of the study group

Medical characteristics	Obtained values n (%)
Duration of schizophrenia per patient (in years): [(X ± SD; med (min–max)]	17.79 ± 9.59; 16.5 (2–45)
Number of previous hospitalizations per patient: [(X ± SD; med (min–max)]	9.54 ± 5.15; 8.5 (1–25)
Number of psychotropic medications per patient: [(X ± SD; med (min–max)]	4.18 ± 1.07; 4 (2–7)
Number of antipsychotics per patient: [(X ± SD; med (min–max)]	1.56 ± 0.57; 2 (1–3)
Mood stabilizers:	
no	11 (21.2)
yes	41 (78.8)
Hypnotics:	
no	34 (65.4)
yes	18 (34.6)
Anxiolytics:	
no	7 (13.5)
yes	45 (86.5)
Antidepressants:	
no	48 (92.3)
yes	4 (7.7)
Antiparkinsonics:	
no	22 (42.3)
yes	30 (57.7)

X – mean value; SD – standard deviation

per patient was 1.56 ± 0.57 (range 1–3), and in most cases, patients were also treated with mood stabilizers, anxiolytics, and antiparkinsonics (Table 2).

Most of the study group patients were smokers, brushed their teeth daily, without using oral hygiene aids, in contrast to the control group patients, who were in about 50% smokers, brushed their teeth daily, and used oral hygiene aids in more than 60% (Table 3). In terms of previous dental visits, patients with schizophrenia in most cases visited dentist more than once a year, mostly because of tooth restauration and the pain (Table 3). Patients of the control group visited a dentist in periods shorter than six moths, mostly due to control examinations and dental restoration (Table 3).

In both groups of patients, a statistical significance was observed among partial mobile denture wearers, in terms of the DMFT index, number of carious teeth, CPI modified, and OHI-S (Table 4). The study group patients had significantly higher values of the DMFT index, number of carious teeth, CPI modified, and OHI-S than the control group patients (Table 4). Similarly, a statistically significant difference between groups was observed concerning fixed dentures (crowns and/or bridges) in terms of number of carious teeth, number of filled teeth, CPI modified, and OHI-S (Table 4).

The impact of independent variables (socio-demographic characteristics, characteristics of primary disease, smoking habits, oral hygiene habits and previous dental visits) on oral health indices (DMFT index, CPI modified, and OHI-S) was examined by the linear regression model (Table 5). In terms of the DMFT index, the univariate regression model showed that age, educational level, and the

Table 3. Smoking habits, oral hygiene habits, and previous dental visits of the study group and the control group

Smoking habits, oral hygiene habits, and previous dental visits	Obtained values		Significance[a] (p)
	Study group n (%)	Study group n (%)	
Smoking habits:			
no	13 (25)	24 (46.2)	
yes	39 (75)	28 (53.8)	0.000*
Frequency of brushing teeth:			
no	18 (34.6)	0 (0)	
occasionally	6 (11.5)	0 (0)	
yes	28 (53.8)	52 (100)	0.000*
Tooth brushing technique:			
correct	14 (26.9)	25 (48.1)	
incorrect	38 (73.1)	27 (51.9)	0.000*
Oral hygiene aids:			
no	21 (61.8)	10 (19.2)	
occasionally	13 (38.2)	34 (65.4)	
yes	0 (0)	8 (15.4)	0.026*
Last dental visit:			
less than six months ago	11 (21.2)	23 (44.2)	
six months to one year ago	9 (17.3)	14 (26.9)	
more than one year ago	32 (61.5)	15 (28.8)	0.000*
Reason of the last dental visit:			
control exam	3 (5.8)	17 (32.7)	
tooth restauration	15 (28.8)	19 (36.5)	
pain	13 (25)	0 (0)	
prosthetic rehabilitation	3 (5.8)	1 (1.9)	
oral soft tissue problems	18 (54.5)	15 (28.8)	0.000*

*statistically significant;
[a]Pearson's χ^2 test

use of oral hygiene aids had significant impact on the value of this oral health index (Table 5). However, the multivariate regression model showed that only age of patients had significant impact on the DMFT index value of the study group patients (Table 5). Similarly, univariate regression analysis showed statistical significance of the CPI modified and OHI-S among the study group patients in terms of gender, number of previous hospitalizations, and the use of oral hygiene aids for CPI modified, and tooth brushing technique and oral hygiene aids for OHI-S. In terms of CPI modified, multivariate regression model showed that all three independent variables had a significant impact on the value of this oral parameter. In terms of OHI-S, multivariate regression model showed that only tooth brushing technique had a significant impact on the value of this index (Table 5).

DISCUSSION

The average values of the DMFT index, CPI modified, and OHI-S among patients with schizophrenia who had prosthetic appliances were significantly higher than that of the control group patients, which is in accordance with previous studies [8, 9, 10, 16, 17, 18].

In terms of socio-demographic characteristics of patients with schizophrenia, this study showed that they had lower educational level and were mostly unemployed, unmarried, and lived with their parents, which lead to financial deficit. It is known that patients with schizophrenia have problems with financial competence, leading to deficit in several cognitive functions that have an important role in maintaining an independent social life [19].

In the study group patients, schizophrenia lasted in average 17.79 ± 9.59 years, with the large number of hospitalizations per patient (over 10 on average), which points to the fact that patients were hospitalized for a proportionally long time period, as shown in other studies as well [8, 18]. Also, they were predominantly treated with antipsychotics: typical or first-generation, and atypical or second-generation. Although both groups of antipsychotics block dopamine receptors, atypical ones differ from the typical since they have a more secure profile of neurological side effect and are less likely to cause extrapyramidal symptoms, such as parkinsonism, expressed by muscle rigidity and involuntary and intentional tremors [20]. These deficiencies of the first-generation antipsychotics have a negative effect on fine motor movements and, consequently, on the patient's ability to efficiently brush

Table 4. Oral health indices of the study group and the control group

Dentures	Study group X ± SD; Med (min–max)	Control group X ± SD; Med (min–max)	Significance[a] (p)
Partial mobile denture			
DMFT index	20.96 ± 4.70; 22 (8–28)	15.18 ± 3.03; 16 (10–20)	0.000*
carious teeth	6.31 ± 4.00; 6 (0–13)	0.55 ± 1.21; 0 (0–4)	0.000*
missing teeth	11.42 ± 6.44; 10 (6–23)	10.81 ± 5.10; 11 (5–19)	0.781
filled teeth	3.23 ± 3.50; 1.5 (0–11)	3.81 ± 3.57; 4 (0–10)	0.612
CPI-modified	2.35 ± 0.85; 2 (1–4)	1.00 ± 0.45; 1 (0–2)	0.000*
OHI-S	2.23 ± 0.82; 2 (0–3)	0.36 ± 0.50; 0 (0–1)	0.000*
Fixed denture (crowns and/or bridges)			
DMFT index	14.87 ± 6.52; 15 (5–28)	12.78 ± 5.08; 12.5 (4–24)	0.293
carious teeth	6.80 ± 5.29; 5 (2–20)	1.70 ± 2.05; 1 (0–8)	0.000*
missing teeth	3.87 ± 2.55; 3 (2–10)	2.90 ± 2.55; 3 (1–10)	0.407
filled teeth	4.20 ± 4.04; 4 (0–12)	8.18 ± 4.08; 7 (2–19)	0.004*
CPI-modified	1.87 ± 6.40; 2 (1–3)	0.85 ± 0.92; 1 (0–3)	0.000*
OHI-S	1.67 ± 0.72; 2 (0–3)	0.45 ± 0.55; 0 (0–2)	0.000*

DMFT – Decayed, Missing and Filled Teeth Index; CPI – Community Periodontal Index; OHI-S –Simplified Oral Hygiene Index; X – mean value; SD – standard deviation;
*statistically significant;
[a]Mann–Whitney test

Table 5. The values of oral parametar indices among the study group examined by the linear regression models

Parameters	DMFT index				CPI modified				OHI-S			
	Univariate linear regression analysis		Multivariate linear regression analysis		Univariate linear regression analysis		Multivariate linear regression analysis		Univariate linear regression analysis		Multivariate linear regression analysis	
	#B (95% CI)	p	#B (95% CI)	p	#B (95% CI)	p	#B (95% CI)	p	#B (95% CI)	p	#B (95% CI)	p
Gender	-0.131	0.947	-		-0.677	0.008*	-0.734	0.004*	0.071	0.788	-	
Age	0.300	0.000*	0.360	0.001*	0.019	0.152	-		0.020	0.104	-	
Education	-2.834	0.004*	-1.416	0.160	-0.158	0.270	-		-0.188	0.165	-	
Employment	0.847	0.267	-		-0.034	0.764	-		0.022	0.841	-	
Marital status	-1.472	0.271	-		-0.118	0.556	-		-0.275	0.139	-	
Residence	-0.481	0.657	-		0.036	0.817	-		0.243	0.109	-	
Duration of schizophrenia	0.126	0.195	-		4.281	0.998	-		0.021	0.109	-	
Number of previous hospitalizations	0.162	0.341	-		0.054	0.044*	0.058	0.022*	0.017	0.498	-	
Number of psychotropic medications	0.147	0.846	-		0.181	0.134	-		-0.025	0.836	-	
Number of antipsychotics	0.946	0.564	-		0.369	0.083	-		-0.137	0.525	-	
Mood stabilizers	-3.042	0.180	-		-0.483	0.149	-		-0.286	0.403	-	
Hypnotics	2.595	0.182	-		0.500	0.058	-		0.249	0.355	-	
Anxyolitics	-4.813	0.074	-		-0.175	0.721	-		-0.776	0.069	-	
Antidepressants	3.042	0.384	-		-0.179	0.762	-		-0.049	0.935	-	
Antiparkinsonics	0.570	0.763	-		0.191	0.460	-		0.176	0.493	-	
Smoking habits	-0.612	0.578	-		-0.247	0.094	-		0.008	0.953	-	
Frequency of brushing teeth	-1.019	0.313	-		-0.125	0.383	-		-0.049	0.731	-	
Tooth brushing technique	3.293	0.113	-		0.447	0.083	-		0.728	0.006*	0.750	0.008*
Oral hygiene aids	6.524	0.004*	2.781	0.191	0.804	0.008*	0.775	0.003*	0.785	0.007*	0.505	0.062
Last dental visit	0.768	0.303	-		-0.004	0.965	-		0.164	0.092	-	
Reason of last dental visit	0.451	0.546	-		0.013	0.900	-		0.084	0.393	-	

DMFT – Decayed, Missing and Filled Teeth Index; CPI – Community Periodontal Index; OHI-S –Simplified Oral Hygiene Index;
#B (95%) – unstandardized coefficient B (95% confidence interval);
*statistically significant

their teeth and perform oral hygiene activities [21]. Also, both types of antipsychotics can cause tardive dyskinesia, but atypical antipsychotics, compared to typical ones, are less likely to do so [21]. Tardive dyskinesia is a parafunctional activity of mastication and tongue musculature that can have a negative effect on the teeth and occlusion [21]. Also, both generations of antipsychotics have anticholinergic side effects, including xerostomia or "dry mouth" [22]. As saliva plays a major role in the prevention of dental caries, xerostomia is a significant risk factor for the appearance of dental caries [22]. Moreover, patients with dry mouth often drink carbonated drinks, which increases the risk of caries occurrence even more [22].

Based on linear regression models and statistically significant independent variables (age for the DMFT index; gender, number of previous hospitalizations and oral hygiene aids for CPI modified; and tooth brushing technique and oral hygiene aids for OHI-S), it seems that schizophrenia indirectly affect oral health of patients with this mental disorder, by reducing their motivation and awareness of the importance of oral health.

In the present study, half of the study group patients had partial mobile dentures, while almost 30% of them had fixed dentures (crowns and/or bridges). Choi et al. [23] suggest that dental prosthetic treatment of patients with schizophrenia would seem reasonable with shortened dental bridge, after restauration of four occluding pairs of premolars which provide sufficient occlusal stability and masticatory function. Also, they suggest that older patients, patients with lower education, and the duration of schizophrenia of more than 10 years should be rehabilitated with removable prosthetic appliances [24]. Fixed dentures (crowns and/or bridges) are the first choice for replacing missing teeth in partially edentulous patients [23]. On the other hand, advanced rehabilitation treatments such as dental implants' placement in patients with schizophrenia are insufficiently described in the scientific literature. Dental implants, rather than removable prosthesis, may be favorable for esthetical outcomes in patients with schizophrenia treated under combined surgical and prosthetic rehabilitation planning. This planning should include the fact that general anesthesia in patients with schizophrenia should be limited [23]. Implant placement in local anesthesia should generally be preferred for people with mental disorders; a consultation with psychiatric specialists on conducting the best patient management should be included when patients with schizophrenia need complex and extensive dental extractions [24, 25].

The limitation of this study is a relatively low number of the study group patients. However, there are few prosthetic rehabilitated patients with schizophrenia, having in mind their low socio-economical characteristics. Also, all of them were patients at the Dr. Laza Lazarević Clinic for Mental Disorders in Belgrade. Thus, it can be assumed

that the situation concerning the oral health of this group of psychiatric patients may be much worse in other psychiatric institutions in Serbia.

CONCLUSION

The population of patients with schizophrenia is experiencing, broadly speaking, the same oral health problems and the same barriers in accessing adequate oral care as the mentally healthy population. There is a complex interrelationship between socio-demographic characteristics, schizophrenia, psychotropic medication, and oral health. High costs of dental treatments constitute the main barrier in complete prosthetic rehabilitation of this group of psychiatric patients.

Conflict of interest: None declared.

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Орално здравље протетски рехабилитованих болесника са схизофренијом

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САЖЕТАК

Увод/Циљ Фактори као што су природа психијатријског поремећаја, дужина хоспитализације и орални нежељени ефекти психотропних лекова могу знатно допринети повећаној преваленцији оралних болести код особа са схизофренијом и последичној потреби за протетском рехабилитацијом.

Циљ овог истраживања био је да се установи ниво оралног здравља протетски рехабилитованих болесника са схизофренијом, те размотре могућности и потребе за унапређењем њихове протетске рехабилитације у будућности.

Методе Студијску групу чинила су 52 болесника са схизофренијом, хоспитализована на Клиници за психијатријске болести „Др Лаза Лазаревић" Београд. Контролну групу чинила су 52 болесника, без историје менталних поремећаја, која су лечена на Стоматолошком факултету Универзитета у Београду. Индекси оралног здравља (КЕП индекс, индекс стања периодонцијума у заједници и потребних третмана – *CPITN* и поједностављени индекс оралне хигијене – *OHI-S*), социодемографске карактеристике, пушење, навике у одржавању оралне хигијене и претходне посете стоматологу регистроване су у обе групе испитаника, као и медицинске карактеристике примарне болести код болесника студијске групе.

Резултати Педесет процената испитаника студијске групе имало је парцијалне мобилне протезе, док је готово 30% њих имало фиксне протетске радове, за разлику од контролне групе испитаника, који су претежно (76,9%) имали фиксне протетске радове. У обе групе испитаника уочена је статистичка значајност међу носиоцима парцијалних мобилних и фиксних протетских радова, у смислу КЕП индекса, броја каријесних зуба, *CPITN* и *OHI-S*. Слично томе, уочена је статистички значајна разлика између носилаца фиксних протетских радова у студијској и контролној групи у погледу броја каријесних зуба, рестаурисаних зуба, *CPITN* и *OHI-S*.

Закључак За потпуну оралну и протетску рехабилитацију ове групе психијатријских болесника потребан је мултидисциплинарни приступ.

Кључне речи: протетика; схизофренија; орално здравље

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical analysis of peritonitis in peritoneal dialysis patients

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SUMMARY

Introduction/Objective Peritoneal dialysis is a method of treating patients in the terminal phase of renal failure (end-stage renal disease). Peritonitis represents most severe and most common complication of peritoneal dialysis. The most common peritonitis causes are Gram negative microorganisms: *Staphylococcus-coagulase-negative, Staphylococcus aureus, Streptococcus sp, Neisseria sp.* Gram negative microorganisms are: *Pseudomonas sp, Enterococcus, Klebsiella sp, Proteus sp, Acinetobacter sp.*
The aim of the study was to examine the incidence of peritonitis and to determine the differences between patients with and without peritonitis and catheter infection. Other goals of the work were: the most frequent causes of peritonitis, the outcome of treatment, the influence of the length of treatment on the development of peritonitis, the influence of the peritoneal dialysis adequacy on the development of peritonitis, the influence of anemia, nutritional status, iron status, secondary hyperparathyroidism (Ca, P, $CaxPO_4$, parathormone), protein status – albumin and the effect of acid uricum on the development of peritonitis.

Methods Retrospectively, 84 patients were analyzed of peritoneal dialysis (2012–2016) at the Kragujevac Center for Nephrology and Dialysis of Clinical Center. The diagnosis of peritonitis was based on clinical picture, biochemical analyses, leukocyte in sediment of dialysis, findings of peritoneal-culture, signs of inflammation (C-reactive protein, leukocytes). The analysis included: the most common causes, the outcome of treatment, the influence of the length of treatment, the influence of the peritoneal dialysis adequacy, the influence of anemia, the influence of iron status, the influence of secondary hyperparathyroidism, the influence of protein status - albumin, and the effect of acid uricum on the development of peritonitis.

Results In total, 22 patients had one, six patients had two, six patients had three, six patients more than three episodes of peritonitis. The difference in mean values of the number of erythrocytes, hemoglobin, hematocrit, iron, albumin, diastolic pressure, systolic pressure between patients with peritonitis, and those without it, were statistically significant ($p < 0.05$). The difference in mean values of calcium (Ca), phosphor (P), $CaxPO_4$, uricum value, parathormone, peritoneal dialysis adequacy, systolic pressure was not statistically significant ($p > 0.05$). The incidence of peritonitis and death were not associated ($p = 1.000$).

Conclusion Peritonitis is severe complication of peritoneal dialysis. Anemia and nutritional status are risk factors that affect the development of peritonitis in patients on peritoneal dialysis.

Keywords: patients; peritoneal dialysis; infections; peritonitis; biochemical analysis

INTRODUCTION

Peritoneal dialysis is one of the methods for treating patients in the terminal phase of renal failure (end-stage renal disease) in addition to hemodialysis and kidney transplantation [1]. Peritonitis is the most severe and most common complication of peritoneal dialysis, while severe, prolonged peritonitis can functionally alter peritoneum, which permanently disables the use of peritoneal dialysis [2]. Acute peritoneal dialysis is associated with high incidence of peritonitis (0.5–4%), and in late 1970s, the incidence of peritonitis in patients with chronic peritoneal dialysis was six episodes per year [1, 2]. Sterile peritonitis is non-infectious peritonitis due to the leakage of sterile body fluids into peritoneum (blood, gastric acid, bile, urine, pancreatic secretion) [2]. The symptomatology of peritonitis is linked to the causal trigger, as an entity of inflammation and/or diseases [2]. The knowledge of pathogenesis of infections associated with peritoneal dialysis, possible sources and reservoirs of potential causes are the basis for defining effective protocols, i.e., guidelines for the prevention and control of infections associated with peritoneal dialysis [3, 4]. Infection of catheter exit site and "tunnel" infection are the basic types of the infections [5]. In spite of technological innovations (automatic peritoneal dialysis) in the field of cysts and solutions for peritoneal dialysis, better patient education, introduction of preventive measures, peritonitis remains the leading complication of

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peritoneal dialysis [6]. It is manifested by: diffuse sensitivity of abdominal wall (70%), blurring of dialysis fluid with leukocytes > 100/mm^3 (granulocytes > 50%) and isolation of the dialysis fluid causative agent. For initial diagnosis of peritonitis, two of the three listed criteria must be satisfied by guidelines [6]. The most common causes of peritonitis in patients on peritoneal dialysis are Gram positive microorganisms (50%): *Staphylococcus coagulasa negative*, *Staphylococcus aureus*, *Streptococcus sp*., *Neisseria sp*. Gram negative microorganisms are present (15%): *Pseudomonas sp*., *Enterococcus*, *Klebsiella sp*., *Proteus sp*., *Acinetobacter sp*. *Polymicrobial infections*. Gram positive and/or Gram negative microorganisms are represented by 1–4%, while fungal infections are less frequent < 2% [7, 8, 9]. The microbiological diagnosis of peritonitis implies: the dialysate culture should be taken before susceptible peritonitis, and the first blurred bag is the best sample (50 ml of dialysis); delaying a few hours from the sampling time to the time of planting; staining of Gram negative sediment from the dialysis bag proves the presence of microorganisms in 20–30% of cases; microbiological cultivation of a dialysis sample for determining the cause, and antibiotic therapy [10]. Laboratory signs of peritonitis in patients on peritoneal dialysis are: > 100 Le/mm^3 and neutrophil dominance (> 50%); lymphocyte domination in fungal peritonitis; tunnel infection (10%) and less than < 100 Le/mm^3); leukocytosis 10000–15000 Le. [11]. "Tunnel" infection of the exit site may be affected by erythema, edema and skin sensitivity above the pathway of catheter. Many authors have evaluated the role of various catheter implantation techniques and catheter types in lowering the risk of peritonitis in patients [12, 13]. Indications for catheter removal are: refractory peritonitis; relapse peritonitis; peritonitis associated with infection of catheter exit site, i.e., "tunnel" infection; fungal peritonitis; repeated peritonitis caused by: mycobacteria or multiple enteric microorganisms [14]. After the adequate diagnoses of peritonitis (recommended criteria for diagnoses), it is decided to treat it with appropriate antibiotics: first empirical therapy, and later it is adjusted to antibiogram [15]. The duration of therapy, if the effluent is rapidly clear, is about two weeks. In cases where the response to therapy is not adequate, the removal of the peritoneal catheter is advised five days since the treatment beginning [15]. The aim was to analyze the incidence of peritonitis and to determine the differences between patients with and without peritonitis and catheter infection.

METHODS

Patients

Retrospectively, 84 patients (55 women median age: 59.9, 34–86 years, and 29 men median age: 63.06, 36–79 years) were treated with continuous ambulatory peritoneal dialysis 2012–2016 at the Center for Nephrology and Dialysis at the Clinical Center of Kragujevac in Kragujevac, Serbia. The study was performed in accordance with the Declaration of Helsinki, with the approval of local ethics committee on human research (Clinical Center of Kragujevac, Serbia) and informed consent was obtained from each study participant. The diagnosis of peritonitis was made in accordance with the recommended guidelines from the above references. All patients started treatment with empirical therapy according to the guidelines for the treatment of peritonitis in patients on peritoneal dialysis, or if it was relapsed to earlier sensitivity, and upon the arrival of the dialysate culture, the antibiotic was changed to the antibiogram. Peritonitis was treated for two to three weeks depending on the cause and rate of withdrawal symptoms (one peritonitis was treated for more than three weeks with the protection of a fungi, two episodes caused by the *Candida* were recorded).

Clinical parameters

The diagnosis of peritonitis was based on the clinical picture e.g., turbid dialysis fluid, abdominal pain, sensitivity of the abdomen to palpation, high body temperature, vomiting, fever and diarrhea.

Laboratory parameters

The number of leukocytes in sediment of dialysate, the findings of peritoneal dialysis culture and the signs of inflammation such as C-reactive protein, the number of leukocytes, etc. Our analysis included: the most common causes, the outcome of treatment, the influence of the length of the treatment, the influence of peritoneal dialysis adequacy, the influence of anemia, the influence of iron status, the influence of secondary hyperparathyroidism, the influence of protein status (albumin) and the effect of acid uricum on the development of peritonitis. Preliminary results were known after two to three days, definitive after five days of sewing. C-reactive protein was determined by an immune-nephelometric assay (Dade-Behring, BN II, Marburg, Germany). Hematological parameters (anemia, nutritional status) were determined using LH750 hematologic analyzer (Beckman Coulter Inc., Brea, CA, USA).

Adequacy of peritoneal dialysis

Adequate chronic peritoneal dialysis implies a prescribed dialysis procedure to ensure a good quality of life of the patient, the absence of physical problems and morbidity and mortality, which are similar to those of the healthy population. The most commonly used parameter for the minimum acceptable weekly values of Kt/V that indicates creatinine clearance according to the American National Kidney Foundation Dialysis Outcome Quality Initiatives recommendations in patients on continuous ambulatory peritoneal dialysis are 1.7 L, or 60 L/1.73 m^2. For patients on continuous cycling peritoneal dialysis and nightly intermittent peritoneal dialysis, given their intermittent character, the mentioned values are even higher, and are 2.0 L or 2.2 L, and for creatinine clearance 63 or 66 L/1.73 m^2 [20, 21].

The statistical methods included: the mean values of numerical variables between two populations using Student's

t-test and Mann–Whitney test; the categorical variables using χ^2 test for contingency tables and Fisher test, too. This article presents the measures of descriptive statistics: arithmetic mean, standard deviation, frequency and percentages.

RESULTS

In the observation period, peritonitis was diagnosed in 40 (47.6%) patients, while 18 (21.4%) patients did not have peritonitis and 26 (31%) had "sterile" peritonitis in rest (55 women and 29 men; middle-aged of 61.48 ± 2.81 years). Gender, age and occurrence of peritonitis were not statistically related (p = 0.624; p = 0.631). Also, the duration of peritoneal dialysis was not correlated with the occurrence of peritonitis (Table 1).

The most common causes of peritonitis in our patients were: *Staohylococus aureus* (18), *Staohylococus coagulase negative* (10), *E.Colli* (six), *Pseudomonas aeruginosa* (three), *Enterococcus sp.* (three), while other causative agents were rarely represented (Table 2).

Table 1. Demographic characteristics of patients with and without peritonitis

Parameters	With peritonitis	Without peritonitis	p
Gender Male (n) Female (n)	 19 21	 10 7	**0.565**
Age mean ± st.dev.	61.6 ± 12.9	62.2 ± 14.2	**0.998**
Duration of peritoneal dialysis (n of months)	38.3 ±27.4	37.7 ±32.1	**0.976**
Primary disease Diabetes mellitus (n) Hypertension (n) Other disease (n)	 13 18 9	 9 6 2	> **0.05**

Table 2. Distribution of microorganisms isolated from the peritoneum of patients on peritoneal dialysis

Causative agents of infection	n	%
Staphylococcus aureus	18	45
Coagulasa negativni staphylococcus	10	25
E. coli	6	15
Pseudomonas sp.	3	7.5
Enterococcus	3	7.5
Total	40	100

Nine infections of the outlet were identified during the analyzed period, four of them were associated with peritonitis. The most common causes of infection were *Staohylococcus aureus* (four patients), *Staohylococcus coagulase negative* (two patients), *Pseudomonas aeruginosa* (one patient), *Enterobacter* (one patient), *Achromobacter xylosooxidans* (one patient) (Table 3).

Number of peritonitis: 22 patients had one, six patients with two, six patients with three and six patients with more than three episodes of peritonitis, Figure 1.

The difference in mean values of the number of erythrocytes, hemoglobin, hematocrit, iron, albumin, diastolic pressure, systolic pressure between patients with

Table 3. Causes of infections catheter exit site of peritoneal catheter in patients

Causative agents of catheter exit site infection	Number of catheter outlet infections	Percentage
Staphylococcus aureus	4	44.5
Staphylococcus spp.	2	22.2
Pseudomonas	1	11.1
Enterococcus	1	11.1
Achromobacter xylosoxidans	1	11.1
Total	9	100

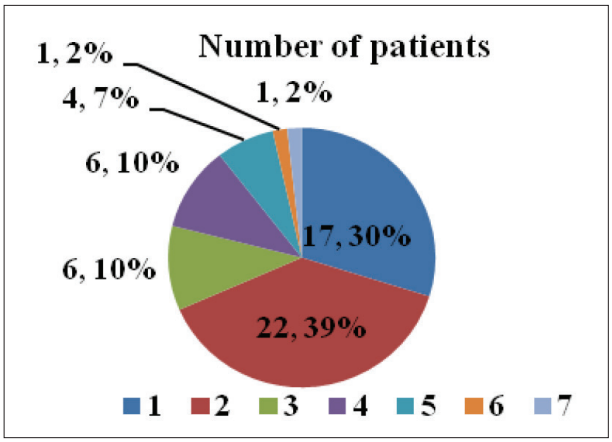

Figure 1. Number of patients with number of episodes of peritonitis

peritonitis, and those without it, statistically were significant and showed in Table 4 (p < 0.05). The difference in mean values of calcium (Ca), phosphor (P), $CaxPO_4$, uricum value, parathormone, peritoneal dialysis adequacy, systolic pressure was not statistically significant (p > 0.05).

Table 4. Variables that affect the occurrence of peritonitis

Variables	With peritonitis	Without peritonitis	p
Erythrocyte	3.09 ± 0.68	3.67 ± 0.97	0.013**
Hemoglobin	97.45 ± 11.7	106.47 ± 15.977	0.021**
Hematocrit	0.28 ± 0.40	0.34 ± 0.07	0.005***
Iron	10.04 ± 4.13	12.51 ± 4.04	0.004***
Albumin	25.13 ± 5.12	30.59 ± 5.33	0.001***
Diastolic pressure	73.12 ± 11.59	78.59 ± 6.86	0.036**
Systolic pressure	124.95 ± 28.64	140.59 ± 18.78	0.044**

The incidence of peritonitis and death were not associated (Table 5, p = 1.000). However, mortality by binary logistic regression was shown to be statistically significantly influenced by the following factors: treatment length, heart rate, erythrocyte, hemoglobin and urea values (Table 5, p < 0.05). Multivariate binary logistic regression showed a simultaneous effect of multiple variables on mortality (erythrocyte count (p = 0.016), iron (p = 0.018) and urea (p = 0.004)). The risk ratio for erythrocyte count is 0.127 (0.024–0.681). The risk ratio for iron is 0.618 (0.416–0.920). The risk ratio for urea is 1.253 (1.053–1.282). With the simultaneous influence of heart rate, erythrocyte count, iron and urea at death, the influence of heart rate is not statistically significant.

Also, mortality by cross tabulation was shown to be statistically significantly influenced by primary disease

Table 5. Variables that affect mortality

Variable	Fatal outcome 0 Mean (SD)	Fatal outcome 1 Mean (SD)	Statistics	
			Z statistics	Sig. p
Treatment length	43.86 (29.8)	14.86 (10.65)	-2.497	0.013**
Pulse	85.25 (20.21)	73.38 (9.12)	-2.441	0.015**
Erythrocyte	3.41 (0.86)	2.77 (0.29)	-3.995	0.000***
Hemoglobin	102.02 (1379)	93.77 (11.28)	-2.143	0.032**
Urea	15.96 (6.72)	24.27 (7.98)	-2.986	0.003**
Albumin	11.48 (4.19)	8.37 (3.51)	-1.875	0.061
Iron	27.59 (5.7)	23.83 (4.97)	-1.821	0.069
Peritonitis Yes No	n of patients with fatal outcome 11 4	n of patients without fatal outcome 29 13		1.000[a]

[a] χ^2 Test

Table 6. Primary disease that affects mortality

Primary disease	Fatal outcome number of patients	Survival number of patients	p
Diabetes mellitus	10	12	0.05*
Hypertension	5	19	0.075
Other disease	0	53	> 0.05

e.g., patients that had diabetes mellitus had statistically significantly increased mortality (Table 6).

DISCUSSION

During analyzed period, 84 patients were treated with peritoneal dialysis, 40 of them had 80 episodes of peritonitis, which is more than the recommended and by the newest guidelines. The most common causes of peritonitis in our patients were: *Staphylococcus aureus*, *Staphylococcus coagulasa negative* and *Escherichia coli*. The incidence of peritonitis decreases was in one for eight and 24 months of the treatment. The significance of peritonitis prevention, quality patient training for independent examination of treatment technique, technological innovations in field of cysts and solutions further reduce the incidence of peritonitis. The incidence of peritonitis in patients in Canada was one episode at 26 patient-months (1996–2005) [16].

In France, one episode was in 29 patient-months (2000–2007) [17]. In the United Kingdom, one episode was in 14 patient-months (2002–2003) [18]. In Latin America, the incidence of peritonitis was one episode in 26 patient-months [19]. "Sterile" peritonitis or culture-negative peritonitis (25.8%) was more commonly reported in our patients, than in patients of other authors – Szeto et al. [20] (17.9%). The other peritonitises were rarely represented as *Streptococcus*-peritonitis (10.3%), *Pseudomonas*-peritonitis (6.9%), *Enterococcus*-peritonitis (4%), *E. coli*-peritonitis (3.4%) [21]. In our patients, the peritonitis caused by *Pseudomonas* were less common than reported by Szeto [20, 21], who found 13.2% peritonitis caused by this causative factor. Szeto et al. [20, 21] found 9.5% of peritonitis associated with infection of the exit site, in the peritonitis caused by *Staphylococcus coagulase negative*, 24.5% in *Staphylococcus aureus*-induced peritonitis [21] and 45.2% in *Pseudomonas*-induced peritonitis [22]. The most common causes of infection of peritoneal catheter exit site were *Staphylococcus aureus* in four patients, and *Staphylococcus coagulase negative* in two patients [22]. In our patients, there were fewer outbreaks of infection during the analyzed period, compared to the other authors, and in particular associated with severe peritonitis. In Australia, Govindarajulu S et al. [23] found 14% of peritonitis caused by *Staphylococcus aureus*. In our patients, the frequency of peritonitis caused by *Staphylococcus aureus* was 9.9%, because it is cause of severe peritonitis with worse prognosis. In Australian patients [23], *Pseudomonas* infections were less common (2.1%), with *E. coli* (6.3%) and *Klebsiella* (4%) more often than in our patients. Fungal infections were not frequent in our center: only two patients had this infection (1.1%), while experts in Australia accounted for 3.1% of fungal peritonitis [23]. A particular problem in all patients on dialysis is anemia [24]. Previous studies showed that patients on peritoneal dialysis had anemia, but less pronounced anemia syndrome than patients undergoing repeated hemodialysis. This beneficial effect of peritoneal dialysis can be explained by higher erythropoietin concentrations, reduced concentration of erythropoiesis-inhibitors and higher quality of nutrition (respectively nutritional status). It is now believed that significant difference in severity of anemia among patients on treatment with peritoneal dialysis and hemodialysis was associated with better clearance of middle molecules, which are essential inhibition factors of the same [24, 25]. During the five-year analyzed period by examining impact of anemia on development of peritonitis, we found that anemia was significant risk factor for the development of peritonitis. The other factors that increase risk of peritonitis include: age, diabetes mellitus, obesity, cardiovascular disease, depression, catheter linkage and/or catheter infections [26]. Prevention of peritonitis associated with peritoneal dialysis represents the high treatment priority [27]. Clinical practice patterns are very different today. Intravenous vancomycin may reduce the risk of early peritonitis and peri-operative treatments. Antifungal prophylaxis with oral nystatin or oral fluconazole may also reduce risk of fungal peritonitis. Another antimicrobial therapy has not shown the adequate efficacy [27]. In Japan, developing effective outpatient protocols for peritonitis treatment and ready and prompt access to home-administered intra-peritoneal antibiotics may reduce the costs associated with peritonitis treatment and peritoneal dialysis therapy. [28]. The authors suggest that biological status of iron in patients on peritoneal dialysis may be a risk factor for the development of infectious peritonitis (improving growth of bacteria through transferring-iron) [29]. Also, in accordance with our results about peritonitis influence on mortality, Tekkarismaz et al. [30] have shown that peritonitis did not reduce patient survival.

CONCLUSION

In the five-year analyze period, 84 patients were treated with peritoneal dialysis and 40 patients had 80 episodes of peritonitis. Anemia, nutritional status, biological status of iron and protein status (albumin) were risk factors which influenced on the development of peritonitis in our patients with peritoneal dialysis. Secondary hyperparathyroidism (Ca, P, CaxPO_4, parathormone), increased acid uricum and the length of peritoneal dialysis treatment or the adequacy of dialysis had no statistically significant effect on the development of peritonitis in our patients who were treated with peritoneal dialysis.

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Клиничка анализа перитонитиса код болесника на перитонеумској дијализи

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САЖЕТАК

Увод/Циљ Перитонеумска дијализа је начин лечења болесника у терминалној фази бубрежне слабости (крајњи стадијум бубрежне болести). Перитонитис представља најтежу, најчешћу компликацију перитонеумске дијализе. Најчешћи изазивачи перитонитиса су грам-позитивни микроорганизми: *Staphylococcus-coagulasa-negativ., Staphylococcus aureus, Streptococcus sp., Neisseria sp.* Грам-негативни микроорганизми су: *Pseudomonas sp., Enterococcus, Klebsiella sp., Proteus sp., Acinetobacter sp.*

Циљ студије је био да се испита учесталост перитонитиса и утврде разлике између болесника са перитонитисом и без њега и инфекције због катетера. Остали циљеви рада били су одредити најчешће узроке перитонитиса, исход лечења, утицај дужине лечења на развој перитонитиса, утицај адекватности перитонеумске дијализе на развој перитонитиса, утицај анемије, нутритивни статус, статус гвожђа, секундарни хиперпаратиреоидизам (*Ca*, *P*, *CaxPO*$_4$, паратхормон), статус протеина – албумин и утицај мокраћне киселине на развој перитонитиса.

Методе Ретроспективно је анализирано 84 болесника на перитонеумској дијализи од 2012. до 2016. године у Центру за нефрологију и дијализу Клиничког центра Крагујевац. Дијагноза перитонитиса постављена је на основу клиничке слике, леукоцита у седименту дијализата, налаза културе перитонеумског дијализата, присутних знакова инфламације (це-реактивни протеин, леукоцити). Анализа је обухватала најчешће узрочнике, исход лечења, утицај дужине лечења, утицај адекватности перитонеумске дијализе, утицај анемије, утицај статуса гвожђа, утицај секундарног хиперпаратиреоидизма, утицај протеинског статуса – албумина и утицај мокраћне киселине на развој перитонитиса.

Резултати Двадесет два болесника су имала једну епизоду перитонитиса, шест болесника две, шест болесника три и шест болесника више од три епизоде перитонитиса. Разлика у средњим вредностима броја еритроцита, хемоглобина, хематокрита, гвожђа, албумина, дијастолног притиска, систолног притиска између болесника са перитонитисом и оних без њега биле су статистички значајне ($p < 0,05$).

Разлика у средњим вредностима калцијума (*Ca*), фосфора (*P*), *CaxPO4*, вредности мокраћне киселине, паратхормона, адекватности перитонеалне дијализе, систолног притиска нису биле статистички значајне ($p > 0,05$). Инциденца перитонитиса и смртни исход нису повезани ($p = 1,000$).

Закључак Перитонитис представља најтежу компликацију перитонеумске дијализе. Анемија и нутритивни статус су фактори ризика који утичу на развој перитонитиса код болесника на перитонеумској дијализи.

Кључне речи: болесници; перитонеална дијализа; инфекције; перитонитис; биохемијске анализе

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The role of adiponectin and its receptor in patients with idiopathic membranous nephropathy complicated with hyperuricemia

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SUMMARY

Introduction/Objective This study aimed to assess the changes of adiponectin (APN), IL-1β, adiponectin receptor 1 (Adipo R1), and NLRP3 expression of patients with idiopathic membranous nephropathy (IMN) complicated with hyperuricemia (HUA) and analyze the relationship between the APN pathway and the NLRP3 pathway.

Methods A group of 48 patients with IMN + HUA, a group of 49 patients with IMN, 30 healthy controls, and 24 samples of healthy renal tissue were evaluated. APN and IL-1β of each group were detected by the ELISA method. AdipoR1 and NLRP3 in kidney tissue were detected by immunohistochemistry. The clinical data of each group were collected, and the relationship between APN, IL-1β, AdipoR1, NLRP3, and other indexes was analyzed.

Results (1) The concentration of UA, APN, IL-1β, and NLRP3 in the IMN + HUA group were significantly higher than those in the IMN group, but the AdipoR1 was lower. (2) With the severity of chronic kidney disease stage, APN, IL-1β, and NLRP3 gradually increased in the IMN + HUA group, but AdipoR1 gradually decreased. However, the aforementioned indicators did not change significantly in the IMN stages.

Conclusion The AdipoR1–AMPK and NLRP3–caspase-1–IL-1β signaling pathway may play an essential role in IMN + HUA patients. An intervention on these two pathways may have significant impact on the disease occurrence and progression in IMN + HUA patients.

Keywords: adiponectin; AdipoR1; NLRP3; idiopathic membrane nephropathy; hyperuricemia

INTRODUCTION

The idiopathic membranous nephropathy (IMN) is a kind of kidney-specific autoimmune glomerular disease, which is a common pathological type of adult nephrotic syndrome [1, 2]. It is well known that hyperuricemia (HUA) in chronic kidney disease (CKD) may aggravate the inflammatory reaction, cause oxidative stress injury, and aggravate the deterioration of renal function.

Adiponectin (APN) is a unique protein secreted by adipocytes, which is involved in glucose, lipid metabolism, and inflammatory reaction. APN has the effects of insulin-sensitizing, anti-inflammation, and anti-atherosclerosis. Some scholars have found that the AdipoR1-AMP-activated protein kinase (AMPK) pathway can maintain the normal physiological homeostasis of the kidney [3]. Serum uric acid (UA) is an independent predictor of the development, progress, and prognosis of primary nephrotic syndrome (PNS) [4–8]. It can induce the overexpression of the nod-like receptor protein 3 (NLRP3) signaling pathway and cause kidney inflammation [9]. Recent studies have shown that UA may first activate the NLRP3 inflammatory pathway, which then triggers APN–AdipoR1 signal transduction to reduce local inflammation in renal proximal tubule epithelial cells (PTECs) [10]. The purpose of this study was to examine the expression of ANP, IL-1β, and AdipoR1, NLRP3 in patients with IMN + HUA and IMN, and to assess the relationship between APN–AdipoR1 pathway and NLRP3–caspase-1–IL-1β pathway. We speculate that high-level UA would initially activate the NLRP3 pathway, followed by the APN pathway, thus triggering renal self-protection in IMN + HUA. A certain degree of UA elevation may be beneficial to renal self-compensation.

METHODS

Participants

The study involved 97 patients with histologically proven IMN who were hospitalized in the period from January 2018 to November 2018 in the Nephrology Department of the Shanxi

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Provincial People's Hospital. This group was divided into two subgroups: IMN + HUA (48 patients) and IMN (49 patients). These subgroups were compared clinically with 30 healthy individuals (plasma and urine) from the medical examination center and histologically with 24 samples (after traumatic nephrectomy) of healthy kidney tissue from the urology department, which represented the control group. The age and sex of the enrolled population may be comparable. All participants in this study signed an informed consent form and were approved by the ethics committee.

Inclusion criteria were as follows: according to the light microscope, there were more than 15 glomeruli in the histological specimens of the patients; estimated glomerular filtration rate (eGFR) > 30 ml/min/1.73 m^2; except glucocorticoid, immunosuppressive, and other drug treatments before the first diagnosis; blood pressure, urine and blood biochemistry were normal in the control group.

Exclusion criteria were as follows: pregnancy, tumor, diabetes, hyperlipidemia, obesity, secondary glomerulonephritis.

General clinical data

The general clinical data of the enrolled group were collected. IMN + HUA and IMN were classified into CKD1–3 according to the K/DOQI stage.

Collection of plasma, urine, and renal tissue

Venous blood and clean morning mid-stream of urine were collected. The samples were centrifuged at 3000 rotations per minute and 15 minutes at an average temperature using a high-speed centrifuge.

After ultrasound-guided renal puncture, kidney tissue specimens were stained and sectioned. The renal tissue wax blocks were classified into 1–3 pathological stages according to Ehrenreich and Churg classification [11].

Determination of APN and IL-1β in plasma and urine by ELISA

Plasma and urine APN and IL-1β were assayed with a commercially available kit (Boster Biological Technology, Ltd). According to the manufacturer, the assay has a measurement range of 1.56–100 ng/ml, a sensitivity of < 60 pg/ml, an intra-assay precision was coefficient of variation (CV) < 5.8%, and inter-assay precision was CV < 6.9% .

AdipoR1, NLRP3 detection with immunohistochemical analysis of kidney tissue

The wax block to be tested was sliced and baked. Then the wax block was processed by immunohistochemistry. Using a high-power microscope (×400), each slice was selected for five fields of view for preservation. Image analysis was performed using Image J software, and five different areas of view of each slice were determined. The average optical density (AOD) was calculated separately, and the average value was taken as the absorbance value of the index measured for each slice.

Statistical analysis

All the data obtained in the study were processed and analyzed by IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA). The mean ± standard deviation or median (interquartile range) was used to describe the econometric data, and the frequency and percentage of the counting data were defined. The comparison of econometric data in two groups was carried by LSD-t-test, a non-parametric test was used to compare the homogeneity of normal variance between the two groups, the χ^2 test was used to compare the qualitative data between different groups, and Spearman analysis was used to analyze the correlation between the two groups.

RESULTS

Patients and controls

Basic data on the studied subjects are presented in Table 1. There were 48 patients with IMN + HUA, and the average age was 47.9 ± 11.6 years old, including 62.5% males and 37.5% females. CKD stage 1 patients accounted for 72.9%, 2–3 stage accounted for 27.1% (CKD4, 5 patients basically no renal biopsy); IMN patients accounted for 64.6% of stage 1, and stage 2–3 accounted for 35.4%. Normal plasma and urine samples were 30 cases, and the average age was 46.7 ± 7.6 years old, including 56.7% for males and 43.3% for females. Basic data on the examined patients grouped according to histological stages of IMN, and controls were shown in Table 2. There were 24 normal renal tissue specimens with an average age of 49.7 ± 11.7 years, of which 66.7% were males, and 33.3% were females. There was no difference in age and sex between groups.

Table 1. Basic data of clinical grouping of plasma and urine samples $\bar{x}\pm s$

Parameter	Control n = 30	IMN + HUA n = 48		IMN n = 49	
		CKD stage 1	CKD stage 2–3	CKD stage 1	CKD stage 2–3
Number	30	35 (72.9%)	13 (27.1%)	29 (59.2%)	20 (40.8%)
Age, years	46.7 ± 7.6	46.9 ± 10.7	50.2 ± 13.9	52.3 ± 9.6	47.2 ± 10.6
Sex, m/f	17/13	22/13	8/5	18/11	14/6

CKD – chronic kidney disease; IMN + HUA – idiopathic membranous nephropathy + hyperuricemia; m – male; f – female

Table 2. Basic data of clinical grouping of renal tissue samples $\bar{x}\pm s$

Parameter	Control n = 24	IMN + HUA n = 48		IMN n = 49	
		IMN Stage 1	IMN Stage 2–3	IMN Stage 1	IMN Stage 2–3
Number	24	31 (64.6%)	17 (35.4%)	29 (59.2%)	20 (40.8%)
Age, years	49.7 ± 11.7	47.7 ± 12.8	48.3 ± 8.6	48.1 ± 9.6	51 ± 11.5
Sex, m/f	16/8	19/12	13/4	19/10	13/7

IMN – idiopathic membranous nephropathy; HUA – hyperuricemia; m – male; f – female

Table 3. Expression of clinical indexes in different groups

Parameter	Healthy group	IMN	IMN + HUA	p
SCr (umol/L)	72 ± 3.2	80.9 ± 22.9[a]	112.9 ± 17.6[a]	0.039*
BUN (mmol/L)	4.9 (4.1,5.8)	5.5(4.5, 7.6)[a]	6.0 (3.9, 9)[a]	0.045*
UA (mmol/L)	339.9 ± 30.4	328.5 ± 57.2[a]	449.8 ± 55.9[a,b]	< 0.001**
eGFR (mL/min per 1.73m^2)	104.3 ± 2.1	96.8 ± 28.2[a]	82.0 ± 23[a,b]	0.01*
Cys-C (mg/L)	0.9 ± 0.1	1.3 ± 0.5[a]	1.3 ± 0.4[a]	< 0.001**
24hUPT	0.08 (0.01, 0.11)	7.4 (5.1, 9.6)[a]	6.4(3.8, 9.3)[a]	< 0.001**

BUN – blood urea nitrogen; UA – uric acid; SCr – serum creatinine; eGFR – glomerular filtration rate; Cys-C – cystatin C; 24hUPT – 24-hour urine protein test;
[a]IMN + HUA and IMN *vs.* control;
[b]IMN + HUA *vs.* IMN

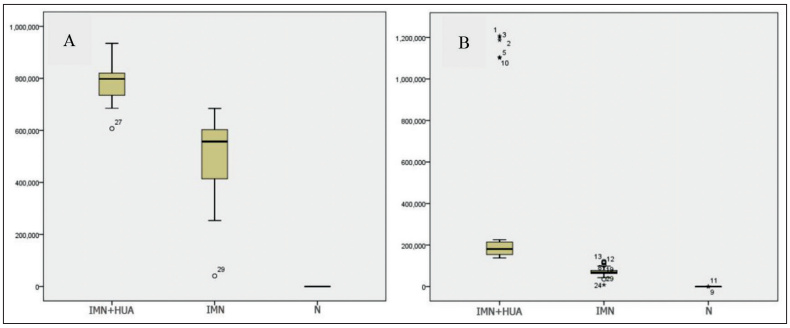

Figure 1. Median values of blood (A) and urinary (B) adiponectin in three patient groups; blood and urine adiponectin values were the highest in the idiopathic membranous nephropathy + hyperuricemia group of studied patients in comparison to others (p = 0.001)

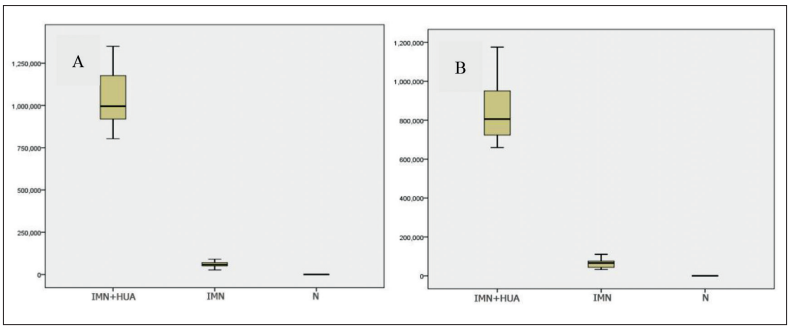

Figure 2. Median values of blood (A) and urinary (B) IL-1β in studied patients; blood and urine IL-1β values were the highest in the idiopathic membranous nephropathy + hyperuricemia group of studied patients in comparison to others (p = 0.001)

Table 4. Analysis of blood and urine among patients with different chronic kidney disease stages and histology stages of IMN + HUA

Staging	CKD 1	CKD 2–3	p	IMN stage 1	IMN stage 2–3	p
n	35	13		31	17	
Sex m/f	22/13	8/5	0.552	17/14	13/4	0.193
Age (years)	46.9 ± 10.7	50.2 ± 13.9	0.551	47.6 ± 13.1	48.3 ± 8.6	0.865
SCr (umol/L)	66.2 ± 12.6	160.9 ± 16.6[a,b]	< 0.001**	90.6 ± 19.1[a]	116.9 ± 13.9[a]	0.032*
BUN (mmol/L)	4.2 (3.5, 5.3)	11.2 (9.4,13.1)[a,b]	< 0.001**	4.7 (3.8, 7.4)[a]	5.3(3.9, 9.4)[a,b]	0.688
eGFR (mL/min per 1.73 m^2)	103.3 ± 14.8	71.6 ± 9.5[a,b]	< 0.001**	89.6 ± 23.2[a]	85.4 ± 21.9[a]	0.02*
Cys-C (mg/L)	1.2 ± 0.3[a]	1.5 ± 0.6[a,b]	< 0.001**	1.2 ± 0.5[a]	1.3 ± 0.3[a]	< 0.001**
24hUPT	6.2 (3.9, 8.1)[a]	8.8 (2.6, 11.3)[a]	0.359	7.1 (3.9, 9.2)[a]	5.7 (2.4, 9.9)[a]	< 0.001**

BUN – blood urea nitrogen; SCr – serum creatinine; eGFR – glomerular filtration rate; Cys-C – cystatin C; 24hUPT – 24-hour urine protein test; CKD – chronic kidney disease;
[a]CKD stages *vs.* control;
[b]CKD stage 1 or IMN stage 1 *vs.* CKD stage 2–3 or IMN stage 2–3

Laboratory data in the studied groups

Basal laboratory analyses are shown in Table 3 and Figures 1 and 2. In comparison to the control group of patients, blood urea nitrogen, uric acid (UA), serum creatinine, CystatinC, 24 h urine protein test (UPT), APN, and IL-1β were significantly higher in the IMN + HUA group (p = 0.039–0.001), while eGFR was lower (p = 0.01). In comparison to the IMN group, the IMN + HUA group of patients had UA, APN, and IL-1β higher (p < 0.001).

NLRP3 and AdipoR1 in renal tissue specimens with immunohistochemical analysis in three studied groups of patients

In comparison to the IMN and the control group, NLRP3 was significantly higher, and AdipoR1 was significantly lower in the IMN + HUA group of patients (p < 0.001) (Figures 3A, 3B). Semi-quantitative analysis by immunohistochemical staining showed that both AdipoR1 and NLRP3 were expressed in PTECs. The disease state reduced the expression of AdipoR1, but increased the expression of NLRP3 (Figure 3C).

Idiopathic membranous nephropathy and hyperuricemia: renal function, histological stages, and adiponectin and IL-1β analyses

Comparison of CKD and histological stages of IMN + HUA are presented in Table 4. As the stage of histological lesions worsens, renal function decreases, as well as 24hUPT. A comparison of APN and IL-1β analyses in blood and urine in patients with different stages of CKD and histological changes in IMN + HUA is shown in Figures 4 and 5. No significant differences were observed among these analyses, except for urinary APN, which was the highest in patients with stage 2–3 CKD and histological stage I of IMN + HUA.

Correlation among examined laboratory analyses (Table 5) showed that APN and IL-1β of IMN + HUA patients were positively correlated with serum creatinine, blood urea nitrogen, UA, and 24hUPT

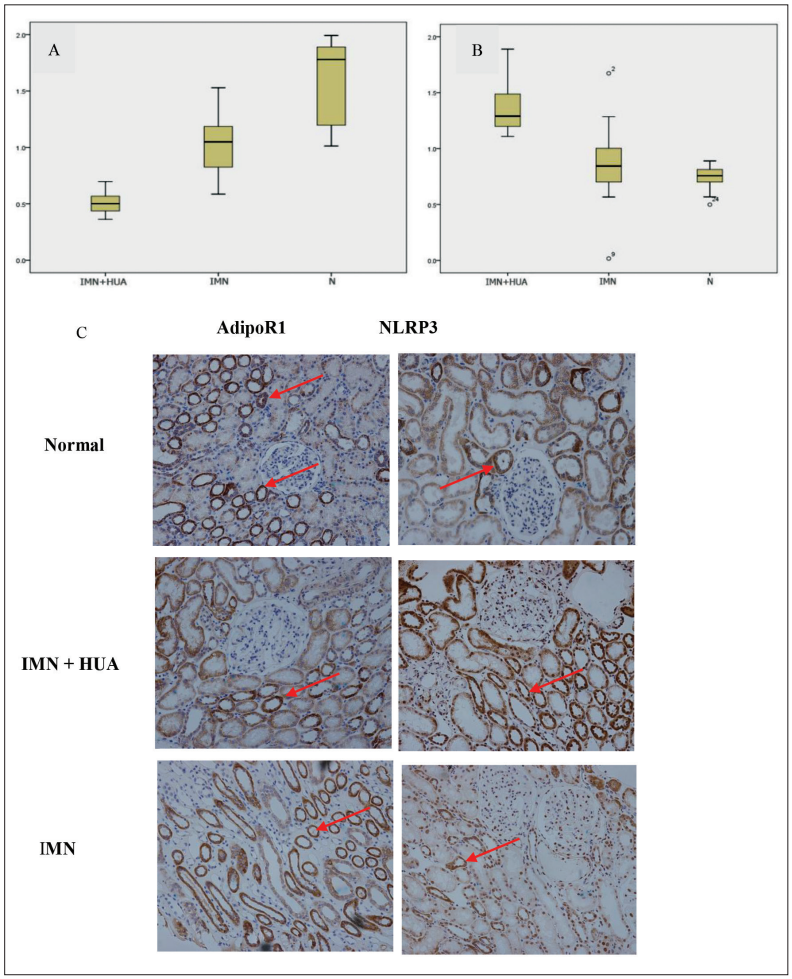

Figure 3. Median values of AdipoR1 (A), NLRP3 (B) and immunostaining (C) in studied patients; AdipoR1 values (A) were the lowest in idiopathic membranous nephropathy + hyperuricemia (IMN+HUA) group of studied patients in comparison to others (p = 0.001), while NLRP3 (B) was the opposite; immunostaining (C) of renal tissue in normal, IMN + HUA, and IMN (×400) (brown and yellow granules are corresponding indexes for immunostaining, respectively), NLRP3 stained most obviously in IMN + HUA, while for AdipoR1 the opposite was true

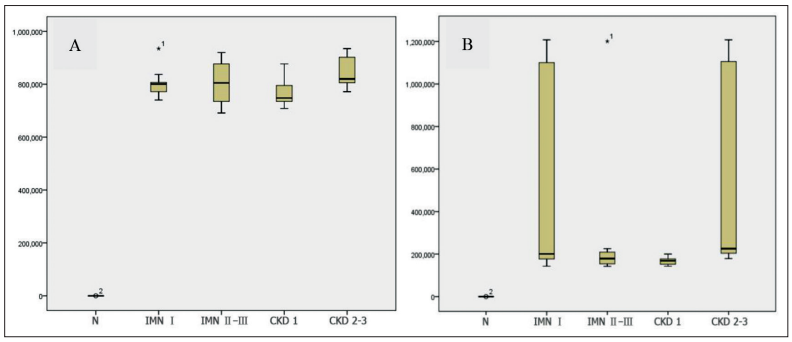

Figure 4. Median values of blood (A) and urinary (B) adiponectin in studied patients; blood and urine adiponectin values were the highest in patients with stage 2–3 CKD and histological stage I of idiopathic membranous nephropathy + hyperuricemia in comparison to others (p = 0.001)

($p < 0.05$), negatively correlated with eGFR ($p < 0.05$). IL-1β was positively correlated with APN ($p < 0.05$).

NLRP3 and AdipoR1 in renal tissue specimens with immunohistochemical analysis In IMN + HUA group

Immunohistochemical analysis revealed that progression of CKD was accompanied by a decrease in AdipoR1, while NLRP3 increased gradually (Table 6). There was no significant difference in the AdipoR1 and NLRP3 expression related to the severity of pathological changes in different histological stages of membranous nephropathy ($p > 0.05$).

In addition, the expression of AdipoR1 in PTECs of IMN + HUA was negatively correlated with UA, 24hUPT, NLRP3, APN, and IL-1β (Table 7). NLRP3 was positively correlated with UA, 24hUPT, APN, and IL-1β ($p < 0.05$), and negatively correlated with AdipoR1 ($p < 0.05$) (Figures 6 and 7).

DISCUSSION

In recent years, researchers have shown an increased interest in HUA and PNS. UA is considered a marker of renal dysfunction. More and more studies show that HUA is identified as an independent risk factor for the occurrence and progress of PNS. Therefore, IMN + HUA patients were selected as the subjects.

APN is identified as an adipose-specific protein and primarily secreted by adipocytes.

APN, beyond its actions in metabolic responses such as energy metabolism regulation and insulin-sensitivity, has pleiotropic effects in many diseases. Studies reported expression of AdipoR1 in glomerular endothelial cells, mesangial cells, PTECs, podocytes, while renal expression of AdipoR2 was much lower than that of AdipoR1 [12, 13]. Recent findings revealed that APN involves in protective effects in renal diseases, which can be filtered through the kidney barrier, binding to AdipoR1. Activation of the AMPK pathway after the binding of APN to AdipoR1 inhibits its downstream pathway, significantly resisting stress, inhibiting protein synthesis, and preventing fibrosis [14, 15]. Therefore, the AdipoR1–AMPK pathway plays an important role in maintaining the normal physiological homeostasis of the kidney [3].

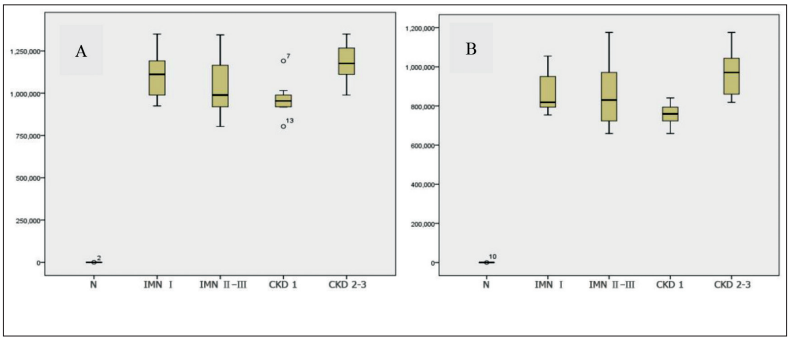

Figure 5. Median values of blood (A) and urinary (B) IL-1β in studied patients; blood and urine IL-1β value were the highest in patients with stage 2–3 CKD of idiopathic membranous nephropathy + hyperuricemia (IMN + HUA) in comparison to others (p = 0.001); no differences in histological stages were found of IMN + HUA

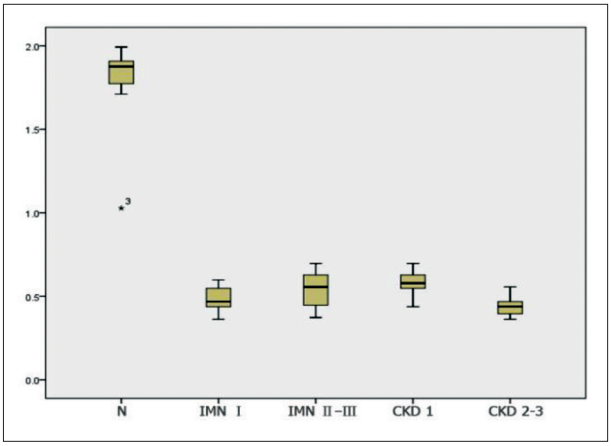

Figure 6. AdipoR1 values were the highest in patients with stage 1 CKD of idiopathic membranous nephropathy + hyperuricemia (IMN + HUA) in comparison to others (p = 0.001); no differences were in histological stage of IMN + HUA

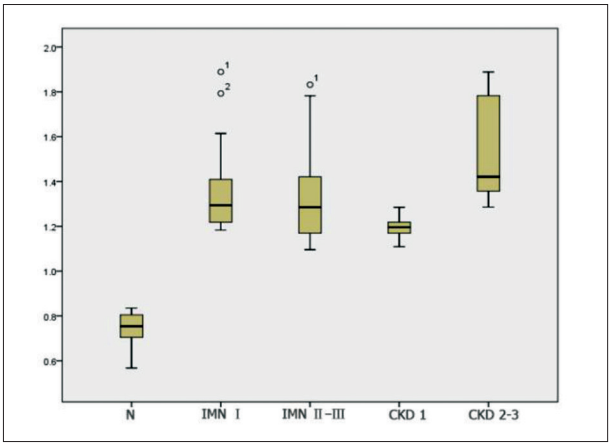

Figure 7. NLRP3 value were the highest in patients with stage 2–3 CKD of idiopathic membranous nephropathy + hyperuricemia (IMN + HUA) in comparison to others (p = 0.001); no histological stage differences were found in IMN + HUA

The study confirmed that the APN decreased in patients with coronary artery disease and metabolic syndrome [16, 17]; still, the APN was at a high level in different stages of CKD [18, 19, 20]. This phenomenon of reverse epidemiology may be related to an inflammatory reaction, vascular injury, body consumption, and insulin resistance [4].

UA has recently been certified as a risk factor for the development, prognosis, and progression of IMN [5, 6, 7, 9, 21, 22], which also leads to kidney inflammation in a lens-dependent and -independent manner [23]. The research showed that UA may firstly activate the NLRP3 inflammatory pathway. After that, APN–AdipoR1 signal transduction triggers to reduce inflammation in the PTECs, which is related to toll-like receptor 4 [10]. We designed this study to determine whether UA affects the development of the IMN + HUA in the same way.

In conclusion, current studies suggested that UA significantly increased APN, AdipoR1 expression, and AMPK phosphorylation in PTECs. Thus, we considered that AdipoR1–AMPK pathway may become a potential therapeutic target for IMN + HUA.

The findings of the present study showed that APN, IL-1β, NLRP3 was higher, and AdipoR1 was lower in the IMN + HUA group in comparison to the IMN group, increasing with the progress of kidney disease, suggesting that the inflammatory state gradually worsened. Hence, we found that UA is a critical activating factor between the AdipoR1–AMPK pathway and NLRP3–caspase-1–IL-1β pathway. Regrettably, there was no apparent difference in the above indicators in the IMN stage. The reason is that IMN stage is based on the stage of kidney pathology under a light microscope. Some pathological changes are between stages 1 and 2, which is difficult to define. To investigate whether this change is specific to IMN, detecting of the anti-PLA2R antibody is helpful. We affirmed that there was no significant correlation between a-PLA2R and all indexes. Thus, we guess that this change is widespread in CKD.

The correlation analysis showed that UA and 24hUPT are the main factors, affecting the expression of NLRP3, AdipoR1, APN, and IL-1β. Our results are similar to a previous study confirming 24hUPT as an independent factor affecting APN [24]. Our study also confirmes that UA correlate to APN, IL-1β, NLRP3, AdipoR1. We speculate that UA may also first activate the NLRP3–IL-1β pathway, induce an inflammatory response, and promote the downstream signaling factors of the NLRP3 pathway to activate the AdipoR1–AMPK pathway, thus producing the body's defense response in IMN + HUA.

Combined with the results of Yang et al. [10], UA can improve the expression of APN and AdipoR1 in mice PTECs. The promotion effect is stronger with the increase of UA concentration. However, what is different from them is that we discovered that the expression of AdipoR1 decreases gradually with the deterioration of renal function in IMN + HUA. APN is negatively correlated with AdipoR1, considering that it is affected by underlying kidney disease, or renal tubular damage leads to a decrease in AdipoR1, or other factors affect AdipoR1 expression. Receptor–ligand activation disorder may be a compensatory process for kidney disease, which can predict disease progression.

In this study, we also found that the APN pathway was closely related to the NLRP3 pathway in IMN + HUA.

Table 5. Correlation analysis between APN, IL-1β, and clinical indexes in IMN + HUA

Parameter		Normal renal tissue control				IMN + HUA				
		SCr	BUN	UA	eGFR	Cys-C	24hUPT	Blood APN	Urine APN	PLA2R
Blood IL-1β	r	0.357	0.569	0.315	-0.458	0.124	0.712	0.827	0.317	0.033
	p	0.013*	< 0.001**	0.009*	0.001*	0.400	< 0.001**	< 0.001**	0.011*	0.38
Urine IL-1β	r	0.293	0.580	0.417	-0.413	0.145	0.712	0.873	0.326	0.017
	p	0.043*	< 0.001**	0.006*	0.004*	0.327	< 0.001**	< 0.001**	0.015*	0.324
Blood APN	r	0.190	0.395	0.691	-0.537	0.015	0.947	-	-	0.110
	p	0.196	0.005*	0.003*	0.005*	0.919	< 0.001**	-	-	0.459
Urine APN	r	0.333	0.437	0.370	-0.340	0.046	0.836	-	-	0.047
	p	0.021*	0.002*	0.047*	0.018*	0.756	< 0.001**	-	-	0.331

BUN – blood urea nitrogen; UA – uric acid; SCr – serum creatinine; eGFR – glomerular filtration rate; Cys-C – cystatin C; 24hUPT – 24-hour urine protein test; APN – adiponectin; IMN + HUA – idiopathic membranous nephropathy + hyperuricemia

Table 6. Difference analysis of renal tissue indexes in patients with different CKD stages and IMN stages IMN + HUA

Staging	Normal renal tissue control	IMN + HUA					
		CKD 1	CKD 2–3	p	IMN Stage 1	IMN Stage 2–3	p
AdipoR1 (AOD value)	1.6 ± 0.4	0.7 ± 0.1[a]	0.5 ± 0.2[a,b]	< 0.001**	0.6 ± 0.2[a]	0.6±0.2[a]	< 0.001**
NLRP3 (AOD value)	0.8 ± 0.1	1.1 ± 0.2[a]	1.4 ± 0.3[a,b]	< 0.001**	1.2 ± 0.2[a]	1.2 ± 0.2[a]	< 0.001**

IMN + HUA – idiopathic membranous nephropathy + hyperuricemia; CKD – chronic kidney disease;
[a]CKD stages *vs.* control;
[b]CKD stage I *vs.* CKD stage 2–3

Table 7. Analysis of the correlation between AdipoR1 and clinical indexes in renal tissue of IMN + HUA

Parameter		SCr	BUN	UA	eGFR	Cys-C	24hUPT	Blood APN	Urine APN	Blood IL-1β	Urine IL-1β	NLRP3	PLA2R
AdipoR1	r	-0.151	-0.317	-0.487	0.494	-0.124	-0.438	-0.855	-0.338	-0.858	-0.892	-0.839	0.092
	p	0.307	0.028*	0.004*	0.007*	0.402	0.005*	0.009*	0.019*	0.008*	0.006*	0.007*	0.17
NLRP3	r	0.378	0.265	0.705	-0.333	0.205	0.522	0.760	0.471	0.771	0.874	-	0.142
	p	0.008*	0.069	0.002*	0.021*	0.161	0.003*	0.002*	0.018*	0.006*	0.005*	-	0.273

BUN – blood urea nitrogen; UA – uric acid; SCr – serum creatinine; eGFR – glomerular filtration rate; Cys-C – cystatin C; 24hUPT – 24-hour urine protein test; APN – adiponectin; IMN + HUA – idiopathic membranous nephropathy + hyperuricemia

Considering that UA should mainly stimulate the production of APN through the NLRP3 pathway, but there are not enough receptors. The body's self-regulation was unbalanced. It is well known that IMN belongs to refractory kidney diseases, and the treatment plan of IMN is only limited to treating with hormone combination immunosuppressants debilitating effect, high recurrence rate, and, if possible, increase in the expression of AdipoR1, or it can be one of the new treatment routes of the IMN + HUA. As for the mechanism that affects AdipoR1 expression, we need to further explore *in vitro* basic experiments.

CONCLUSION

The AdipoR1–AMPK pathway is significantly increased in IMN + HUA, and the prediction of the AdipoR1–AMPK signaling pathway may play an essential role in IMN + HUA, but it is non-specific.

It is speculated that UA may induce self-protection by activating the NLRP3–caspase-1–IL-1β pathway and the AdipoR1–AMPK pathway, but it is essential to improve the expression of AdipoR1 in IMN + HUA.

Conflict of interest: None declared.

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Улога адипонектина и његовог рецептора код болесника са идиопатском мембранозном нефропатијом компликованом хиперурицемијом

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САЖЕТАК

Увод/Циљ Ова студија имала је за циљ да процени промене адипонектина (*APN*), *IL*-1β, рецептор за адипонектин 1 (*AdipoR*1) и *NLRP*3 експресију болесника са идиопатском мембранозном нефропатијом (*IMN*) компликованом хиперурицемијом (*HUA*) и анализира однос између стаза *APN* и стаза *NLRP*3.

Методе Изабрано је 48 болесника са *IMN* + *HUA*, 49 болесника са *IMN*, 30 здравих болесника и анализирана су 24 случаја здравог бубрежног ткива. *APN* и *IL*-1β сваке групе су утврђени методом *ELISA*. *AdipoR*1 и *NLRP*3 у бубрежном ткиву су утврђени имунохистохемијом. Прикупљени су клинички подаци сваке групе и анализирана је веза између *APN*, *IL*-1β, *AdipoR*1, *NLRP*3 и других индекса.

Резултати (1) Нивои експресије *UA*, *APN*, *IL*-1β и *NLRP*3 у групи *IMN* + *HUA* били су значајно виши од оних у групи *IMN*, али ниво експресије *AdipoR*1 је био нижи. (2) У различитим фазама *CKD* и *IMN*, с порастом фазе *CKD*, нивои експресије *APN*, *IL*-1β и *NLRP*3 из групе *IMN* + *HUA* постепено су се повећавали, а ниво експресије *AdipoR*1 постепено се смањивао. Међутим, у фази *IMN* наведени показатељи нису се значајније променили.

Закључак Сигнални пут *AdipoR*1–*AMPK* и *NLRP*3–*caspase*-1–*IL*-1β може играти важну улогу код *IMN* + *HUA* болесника. Интервенција над ова два пута може бити од велике важности за појаву и напредовање болести код болесника са *IMN* + *HUA*.

Кључне речи: адипонектин; *AdipoR*1; *NLRP*3; нефропатија идиопатске мембране; хиперурицемија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Analysis of risk factors for progression of diabetic nephropathy in patients with type 2 diabetes

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SUMMARY

Introduction/Objective The aim of the study was to examine the progression of diabetic nephropathy (DN) in a prospective three-year period as well as to establish the risk factors for DN progression.

Methods The study involved 45 patients with type 2 diabetes and DN (26 males, aged 18–62 years) followed up for three years. All the patients underwent physical examination and laboratory analysis at each visit. Laboratory analyses included complete blood count, serum glucose, urea, creatinine, protein, lipid concentration, glycosylated hemoglobin (HbA1c) and urine protein, albumin and creatinine concentration. Glomerular filtration rate (GFR) was calculated using Modification of Diet in Renal Disease formula. Kidney length and parenchymal thickness were measured by ultrasound.

Results Fasting serum glucose concentration (12.0 ± 2.79 *vs*. 9.50 ± 2.22, p < 0.001) and HbA1c (7.99 ± 1.43 *vs*. 7.49 ± 1.29, p < 0.031) were decreased over the three years. Albuminuria increased (43.75 ± 10.83 *vs*. 144.44 ± 52.70 mg/l, p < 0.001) and GFR (63 *vs*. 58.3 ml/min/1.73 m^2) decreased significantly during the study, but serum lipid concentration remained unchanged. Mean kidney length and parenchymal thickness decreased during the three years. Linear regression analysis found systolic blood pressure, fasting glycemia, HbA1c as positive and kidney length and parenchymal thickness as negative predictors of proteinuria increase, but proteinuria as negative and serum iron and albumin concentrations as positive predictors of annual change in GFR.

Conclusion High blood pressure and high HbA1c are selected as significant risk factors for increasing proteinuria, which is a significant predictor of GFR decreasing in patients with DN.

Keywords: diabetic nephropathy; progression; risk factors

INTRODUCTION

Diabetes mellitus (DM) is a major health problem impairing the quality of life and diminishing the life expectancy of millions of people [1]. The frequency of DM is enormously increasing worldwide, thus more and more people are exposed to the risk of developing diabetic complications. Diabetic nephropathy (DN) is one of the most detrimental consequences of DM regarding patients' quality of life and survival [2]. It affects more than 20% of all diabetic patients, and due to limited therapeutic options it remains the leading cause of chronic kidney disease [3]. DN is a leading cause of end-stage kidney disease (ESKD) in developed countries. The clinical diagnosis of DN is based on the presence of albuminuria and/or reduced estimated glomerular filtration rate (GFR) in the absence of signs or symptoms of other primary causes of kidney damage [4].

International organizations have predicted epidemic proportions of DN and have anticipated that the incidence of DN will dramatically increase by 2050. In addition, DN is associated with a high cardiovascular mortality and frequent development of ESKD [5]. The prevalence of DN patients on regular dialysis in Bosnia and Herzegovina is also increasing and between 2002 and 2014 it has increased from 39.6 to 142 patients per million [6]. The only way to decrease an unceasing rise in the number of patients with DN is persistent implementation of DN prevention and regular screening. The preventive measures should be directed at the risk factors for the occurrence and progression of DN and the screening for DN should begin from the time of diabetes diagnosis as it is observed that about 7% of the patients diagnosed with diabetes already have microalbuminuria [7, 8, 9].

The aims of this study were to examine the progression of DN in a prospective three-year period as well as to establish the risk factors for DN progression.

METHODS

The study involved 45 patients with type 2 diabetes and DN including 26 males and 19 females, with the average age being 61.24 years (18–62 years). The patients were selected from a population of patients with type 2 diabetes and DN who regularly control themselves in the Outpatient Department for Internal Medicine of the University Hospital in Foča,

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both by an endocrinologist and a nephrologist. The criteria for diagnosis of DN were as follows: persistent albuminuria > 300 mg/g creatinine, existence of diabetic retinopathy, exclusion of other kidney or renal tract diseases. The patients who were successively visiting the abovementioned department and whose GFR was above 30 ml/min/1.73 m^2, were included in the study. The patients with any malignancy, serious hepatic failure, those who suffered myocardial infarction or even cerebrovascular insult in the past six months, as well as patients with any kidney disease apart from DN were not included in the study. The selected patients were followed up for three years and only those who came to the control at least once a year during those three years were included in the analysis.

All the patients were interviewed, subjected to physical examination including measuring of blood pressure and calculating body mass index (BMI) and electrocardiography. Physical examination and laboratory analyses were performed at each patient's visit. During the three-year study, we tried to achieve optimal glycoregulation and regulation of blood pressure with the use of renin–angiotensin–aldosterone system inhibitors (RAASi), considering it the basic strategy for slowing down DN progression, but we also advised patients on the importance of diet, physical activity, smoking cessation.

Laboratory analyses were performed at the Department of Biochemistry and Hematology at the Foča University Hospital and they included complete blood count, measuring of creatinine concentration by modified Jaffe method (Beckman Creatinine Analyzer II; Beckman Coulter, Inc., Brea, CA, USA), as well as concentrations of serum glucose, protein, lipid and urine creatinine determined by standard biochemical methods on biochemistry analyzer of the Abbott Laboratories, Chicago, IL, USA (Alcyon Analyzer SA). Glycosylated hemoglobin (HbA1c) is expressed as percentage and determined by using automated high-performance liquid chromatography systems. All laboratory analyses were performed at each patient's visit except serum lipid and blood protein concentrations, which were determined at the beginning and at end of the study. Also, we did not have the opportunity to regularly measure albumin in urine, but all patients underwent this analysis at the beginning of the study because it was one of the criteria for DN.

Urine proteins are expressed by the ratio of urine protein and creatinine concentration (cut off value being 20 mg/mmol). Urine albumins were measured by colorphotometric method with bromocresol green (Olympus AU 400 analyzer, Olympus Co. Ltd., Tokyo, Japan) and expressed by the ratio of albumin and creatinine concentration (cut off value being 3.4 mg/mmol).

GFR was calculated by the Modification of Diet in Renal Disease formula [10]. The progression of DN was assessed on the basis of proteinuria change during the three-year study and expressed by the difference in proteinuria values at the third and first examination. The annual change in GFR was the second indicator of DN progression calculated as the ratio of the difference in GFR at the first and the third examination, divided by the number of years between these examinations.

A kidney ultrasound examination was performed by an experienced doctor in ultrasound diagnostics on a GE LOGIQ P5 ultrasound instrument (GE Healthcare, Chicago, IL, USA) with a 3.5 MHz convex probe. Craniocaudal diameter and parenchymal thickness of the kidney were measured and expressed in millimeters.

Statistical analysis

Continuous variables are presented as the arithmetic mean and standard deviation or as a median and interquartile range depending on the characteristics of the variable, while categorical ones are presented as frequencies. Applying the Kolmogorov–Smirnov test, the type of distribution of all variables was examined. For the analysis, ANOVA with Bonferroni test, Kruskal–Wallis test, Student's t-test, Wilcoxon test and χ^2 test were used as appropriate. Linear regression analysis was used to examine the association of GFR and proteinuria change and demographic, clinical, and laboratory variables.

IBM SPSS Statistics, Version 21.0 for Windows (IBM Corp., Armonk, NY, USA) and MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium) were used for statistical analysis.

This study protocol was done in accordance with the ethical principles of the Declaration of Helsinki. All study participants gave their informed consent and the study was approved by Committee on Ethics of the Foča University Hospital (2/20).

RESULTS

Table 1 shows the main data of examined patients. The average age of the patients at the time of setting the diabetes diagnosis was 51.64 years, while the average diabetes duration was 10.13 years.

Table 1. Main data about the examined patients with diabetic nephropathy at the beginning of the study

Sex, male		26 (57.8%)
Age, years		61.24 ± 11.18
DM duration, years		10.13 ± 7.87
Age at the time of DM diagnosis, years		51. 64 ± 13.03
Type of treatment	Hypoglycemic oral agents	18 (40%)
	Insulin	12 (26.7%)
	Combined	13 (28.9%)
	Missing data	2 (4.4%)
Family history of DM, yes		22 (48.9%)
Cigarette smoking	Yes	6 (13.3%)
	Former smoker	9 (20%)
Alcohol	Yes	8 (17.8%)
Antihypertensive treatment	ACEI	35 (77.8%)
	ARB	5 (11.1%)
	ACEI + CCB	5 (11.1%)

Results are presented as numbers (%) or as mean ± standard deviation; ACEI – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CCB – calcium channel blockers

Table 2. Changes in laboratory parameters, body mass index, and blood pressure in the three-year-long study

Laboratory parameters	1 initial visit	2 after 19.8 ± 2.1 months	3 after 37.7 ± 2.7 months	p		
				1–2	2–3	1–3
Fasting serum glucose, mmol/l	12 ± 2.79	11.9 ± 2.06	9.5 ± 2.22	0.014	0.068	< 0.001
HbA1c %	7.99 ± 1.43	7.81 ± 1.32	7.49 ± 1.29	0.241	0.003	0.031
BMI, kg/m^2	28.47 ± 4.14	29.05 ± 4.4	27.76 ± 4.05	0.156	0.004	0.002
Systolic BP, mmHg	146.44 ± 24.18	141.67 ± 22.21	136.55 ± 12.52	0.144	0.336	0.017
Diastolic BP, mmHg	85.78 ± 9.83	83.44 ± 8.97	82.38 ± 6.56	0.211	0.618	0.038
Urea, mmol/l	8.2 ± 4.3	10.57 ± 6.29	10.22 ± 6.77	0.008	0.698	0.060
Creatinine, µmol/l	98 (88.0–118.5)	100 (84–162)	92.5 (79–129)	0.043	0.939	0.343
GFR, ml/min/1.73 m^2	63 (52–80)	56 (40–85)	58.3 (38.0–89.8)	0.365	0.306	0.030
Erythrocytes × 10^{12}/l	4.28 ± 0.58	4.2 ± 0.69	4.0 ± 0.39	0.770	0.009	0.004
Hemoglobin, g/l	127.5 ± 19.58	120.2 ± 21.96	115.82 ± 14.52	0.015	0.023	< 0.001
Albumins, g/l	36.09 ± 5.65	–	35 ± 4.37	–	–	0.142
Proteins, g/l	63.77 ± 7.24	–	63.5 ± 6	–	–	0.881
Total cholesterol, mmol/l	5.91 ± 1.55	–	5.66 ± 1.31	–	–	0.283
Triglycerides, mmol/l	2.33 ± 0.9	–	2.34 ± 1.03	–	–	0.856
HDL cholesterol, mmol/l	0.9 ± 0.26	–	0.96 ± 0.43	–	–	0.334
LDL cholesterol, mmol/l	3.97 ± 1.38	–	3.76 ± 1.22	–	–	0.244

Data are expressed as mean ± standard deviation or as median and interquartile range; statistical significance of the difference was calculated using Student's t-test and Wilcoxon test;
HbA1C – hemoglobin A1C; BP – blood pressure, HDL – high-density lipoprotein; LDL – low-density lipoprotein; BMI – body mass index

Table 3. Changes in albuminuria, proteinuria, kidney length, and parenchymal thickness in the patients with diabetic nephropathy over three years

Laboratory parameters	1 initial visit	2 after 19.8 ± 2.1 months	3 after 37.7 ± 2.7 months	p		
				1-2	2-3	1-3
U-albumin, mg/l	43.75 ± 10.83	144.44 ± 52.7	–	< 0.001	–	–
U-protein, g/day	0.39 (0.18-1.1)	0.78 (0.44-1)	0.5 (0.27-1.1)	0.006	0.449	0.040
P/Cr, mg/mmol	96.2 (33-152)	143 (59.3-313.9)	136.6 (66.0-352.9)	0.013	0.001	0.039
Right kidney length, mm	117 ± 5.16	114.53 ± 6.61	113.7 ± 7.54	0.007	0.030	0.002
Right kidney parenchymal thickness mm	16.31 ± 2.43	15.63 ± 2.34	15.22 ± 2.22	0.178	0.418	0.037
Left kidney length, mm	118.48 ± 4.61	114.24 ± 18.64	115.94 ± 7.54	0.119	0.523	0.004
Left kidney parenchymal thickness, mm	17.05 ± 3.19	16.31 ± 3.04	15.88 ± 2.57	0.283	0.471	0.046
Mean kidney length, mm	117.88 ± 3.95	115.83 ± 6.07	114.85 ± 7.14	0.010	0.032	0.001
Mean kidney parenchymal thickness, mm	16.79 ± 2.79	16.18 ± 2.75	15.71 ± 2.17	0.299	0.381	0.042

Data are represented as mean ± standard deviation or as median and interquartile range; statistical significance of the difference was calculated using Student's t-test or Wilcoxon test

The patients regularly visited their family physicians, and they visited a nephrologist twice a year. Table 2 shows the values of the monitored parameters recorded on nephrologist examinations at the beginning of the study, in the middle of the study, i.e. after about 18 months, and at the end of the study. Fasting serum glucose concentrations and HbA1c values were above the recommended limit during all three years, although at the very beginning of the study these values were significantly higher than after three years (HbA1c: 7.99 ± 1.43 *vs.* 7.49 ± 1.29, $p < 0.031$). The BMI of patients increased during the first 18 months, and then BMI decreased significantly. Systolic and diastolic blood pressure decreased significantly over the three years. All the patients were on antihypertensive therapy and 77.8% of them used angiotensin-converting enzyme inhibitors, 11.1% angiotensin II receptor blockers, and 11.1% angiotensin II receptor blockers plus calcium channel blockers. There were no changes in the type of antihypertensive drugs during the follow-up but their doses have been changing according to blood pressure values.

During the first 18 months of the study, serum concentration of urea and creatinine increased significantly. The median GFR decreased from 63 ml/min/1.73 m^2 to 58.8 ml/min/1.73 m^2 over the three years and the difference was significant (Table 2).

Albuminuria increased from 43.75 ± 10.83 mg/l to 144.44 ± 52.70 mg/l ($p < 0.001$) and proteinuria from 0.39 g/day to 0.78 g/day ($p = 0.006$) between the first and the second examination, but proteinuria changed insignificantly until the end of the study (Table 3). Kidney length and parenchymal thickness decreased and the dimensions measured at the beginning and end of the study differed significantly.

Table 4 shows the results of linear regression analysis in which the dependent variable was the difference in proteinuria measured at the end and at the beginning of the study, and the independent variables all demographic, clinical, and laboratory variables. Due to the relatively small group and the collinearity among some variables, several models were used in this analysis. Only those variables that are statistically significantly associated with proteinuria change are shown. The analysis identified systolic blood pressure and fasting glycemia at the end of the study as well as HbA1c measured at the second examination as positive

Table 4. Factors associated with the difference in proteinuria at the end and at the beginning of the study.

Parameters	B	p	95% CI
Systolic blood pressure 3, mmHg	6.05	0.049	0.29–12.80
Kidney length 3, cm	-22.05	0.003	-35.98–-8.12
Parenchymal thickness 1, mm	-83.65	0.038	-162.13–-5.16
Fasting plasma glucose 3, mmol/l	72.61	0.024	10.13–135.08
HbA1c % 2	114.75	0.043	4.14–225.35

Table 5. Factors associated with annual change in glomerular filtration rate in patients with diabetic nephropathy (multivariate linear regression analysis)

Parameters	B	p	95% CI
P/Cr 2, mg/mmol	-0.04	0.002	-0.072–-0.02
Iron, mmol/l	1.55	0.007	0.47–2.64
Albumins 2, g/l	1.3	0.032	0.12–2.47

predictors and kidney length at the end of the study and parenchymal thickness at the beginning of the study as negative predictors of difference in proteinuria.

Univariate linear regression analysis was used to select the variables associated with the annual change in GFR. Systolic blood pressure at the end of the study, kidney length and parenchymal thickness both at the beginning and at end of the study, as well as proteinuria at the beginning of the study were identified as negative predictors, while hemoglobin, albumin, and iron concentrations were selected as positive predictors of annual GFR change. These variables, which were found to be significantly associated with GFR change by univariate linear regression analysis, were combined in the multivariate analysis. This analysis identified proteinuria as negative and serum iron and albumin concentrations as positive predictors of annual change in GFR.

DISCUSSION

The main objective of this study was to determine risk factors for DN progression. The study included 45 patients with type 2 diabetes and DN who were followed up for three years. During the three-year follow-up, glycoregulation as well as regulation of hypertension improved significantly. Also, BMI decreased significantly, but serum lipid concentrations did not change. At the same time, GFR was significantly decreased, albuminuria and proteinuria increased, and even kidney length and kidney parenchymal thickness were significantly decreased. Linear regression analysis showed that proteinuria increased more over a three-year period if systolic blood pressure, fasting glycemia and HbA1c were greater and kidney length and parenchymal thickness were lesser. Univariate linear regression analysis showed that the annual decrease in GFR was significantly associated with systolic blood pressure, kidney length and parenchymal thickness, proteinuria, hemoglobin but also serum albumin and iron concentrations. Multivariate analysis identified only proteinuria as negative and serum iron and albumin concentrations as positive significant independent predictors of annual GFR change.

Two major risk factors for the occurrence and progression of DN are hyperglycemia and hypertension. Hyperglycemia is a major pathogenic factor for the occurrence of DN, and numerous studies have confirmed that intensive diabetes therapy and achieving of glycemic target values can prevent or postpone the onset of albuminuria, as well as the progression of DN [11, 12]. Early aggressive treatment of hyperglycemia seems to be important and early favorable glycemic environment is remembered so it is called "metabolic memory" [13]. In the present study, a significant decrease in both fasting glycemia and HbA1c during the three-year follow-up of patients with type 2 diabetes and DN was shown. Both of these biomarkers were also identified by linear regression analysis as predictors of worsening proteinuria. These results confirmed the results of many other studies about the importance of glycoregulation for DN progression. Particularly significant is the fact that better glycoregulation can slow down the progression of DN even if this better glycoregulation is achieved in patients who have had diabetes for many years. In patients included in our study, at the time of study inclusion, diabetes lasted 10.13 years on average, yet in 24.4% of patients, proteinuria did not increase or even decrease, and in 35.5% it increased by less than 100 mg/mmol. Linear regression analysis showed that an increase in proteinuria was associated with fasting glycemia and HbA1c, not with values at the beginning of the study but with values measured at the end of the second or the third year of the study. This indicates that if patients with diabetes lasting more than 10 years achieve better glycoregulation, proteinuria will be affected. Such results have been shown in patients with type 1 diabetes but less frequently in patients with type 2 [14].

In contrast to the association between proteinuria and glycoregulation, there are results on the effect of glycoregulation on GFR. Coca et al. [14], in a large-scale meta-analysis involving 28,065 adult patients with type 2 diabetes, found that intensive glycoregulation did not affect the increase in serum creatinine concentration or the development of ESKD. Similar to these results, our study's linear regression analysis isolated no biomarkers of glycoregulation as significant factors associated with annual GFR change. Coca et al. [14] considered that this lack of association between glycoregulation and changes in GFR was a consequence of the late detection of type 2 diabetes and DN. Therefore, at the time of detection, patients have GFR within normal limits but most probably significant pathomorphological changes in the kidneys. Our results confirmed this assumption. A significant decrease in kidney length and kidney parenchymal thickness was recorded over the course of three years. This decrease could not have happened if there were no morphological changes at the beginning of the study.

Hypertension is another significant risk factor that has been pointed out by numerous studies, and the achievement of target blood pressure has proven to be a significant measure of primary and secondary prevention of DN as well as cardiovascular diseases, the most common cause of death in diabetes [9, 15]. In most patients with type 2 diabetes, hypertension exists even before diabetes is detected.

Our study confirmed the significance of elevated blood pressure for DN progression. Systolic blood pressure at the end of the third year of the prospective study were selected as significant factor associated with both an increase in proteinuria and a decrease in GFR.

RAASi are the standard treatment in the care for hypertensive patients with DM, especially when renal involvement is present [15, 16]. RAASi, even in non-antihypertensive doses, decreased the production of profibrotic factors and directly prevented fibroblast activation [17]. Ramipril may protect the kidneys by suppressing insulin-like growth factor-1 and mitigating the accumulation of renal mesangial matrix [18]. All these findings suggest a novel therapeutic role of RAASi in slowing down of DN progression. In people with advanced chronic kidney disease, stopping renin–angiotensin–aldosterone system inhibition was associated with higher absolute risks of mortality and major adverse cardiovascular events, but also with a lower absolute risk of initiating kidney replacement therapy [19]. There are many RAASi available on the market, but a small number of papers compare the renoprotective effect of different RAASi in patients with DN [20]. Finally, a recent network meta-analysis comparing the effects of antihypertensive agents in diabetic patients with kidney disease showed that combination of fosinopril and amlodipine appeared to be the most efficacious in reducing proteinuria [21].

Although our previous studies have shown that primary care physicians know that RAASi have the greatest renoprotective effect and the greatest number of patients with diabetes and hypertension are treated with RAASi, there is insufficient insistence on achieving the target blood pressure [22]. KDOQI guidelines recommend target blood pressure ≤ 140/90 mmHg for patients with diabetes without proteinuria, while for those with albuminuria blood pressure ≤ 130/80 mmHg is recommended [23]. Our national guidelines recommend that in patients with DN, a target blood pressure lower than 130/80 mmHg may be considered appropriate, dependent on the patient's characteristics, comorbidity or response to therapy [24]. Given that our study included patients who were most commonly in their seventh decade of life and with different comorbidities, we considered blood pressure below 140/90 mmHg to be the targeted one and we achieved this in most patients during the study.

Obesity and arterial hypertension were found in a significant number of patients included in our study. The average BMI was about 27 kg/m^2. Regular check-ups during this prospective study most likely contributed to the fact that the average BMI value significantly decreased over the three years, so BMI does not appear as a significant factor associated with an increase in proteinuria, or a decrease in GFR. This confirms the well-known view that changes in diet and lifestyle, as well as physical activity, which can lead to weight loss, are significant measures of prevention of type 2 diabetes and DN [25].

Dyslipidemia is considered to be one of the factors that affect the progression of DN [26]. Although the concentrations of all four lipids controlled in our patients were higher than those recommended by the guidelines, none of these four lipids were selected as a factor associated with an increase in proteinuria or a reduction in GFR.

The importance of the present study is that, for the first time, risk factors for the occurrence and progression of DN have been examined in the Republic of Srpska and Bosnia and Herzegovina. The major disadvantage of the study is the relatively small number of patients included in the studies. In addition, to examine the progression of DN and its outcome, it would be important that the follow-up period was longer than three years, which would allow establishing not only the deterioration of kidney function but also by the occurrence of ESKD.

CONCLUSION

The study found that type 2 diabetes is discovered late, that patients are burdened with a numerous changeable and unchangeable risk factors for DN. High blood pressure and high HbA1c levels proved to be the most significant risk factors for the progression of DN, while more effective regulation of these factors slowed down its progression.

Conflicts of interest: None declared.

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Анализа фактора ризика за прогресију дијабетесне нефропатије код болесника са дијабетесом типа 2

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САЖЕТАК

Увод/Циљ Циљ рада био је да се испита прогресија дијабетесне нефропатије (ДН) у трогодишњем периоду и да се утврде фактори ризика за прогресију ДН.

Методе Студија је обухватила 45 болесника с дијабетесом типа 2 и ДН (26 мушкараца, старости од 18 до 62 године) који су праћени три године. Свим болесницима су урађени физикални преглед и лабораторијске анализе приликом сваког прегледа. Лабораторијске анализе су укључивале комплетну крвну слику, серумску глукозу, уреу, креатинин, протеине, концентрацију липида, гликозилирани хемоглобин (*HbA1c*), концентрацију протеина, албумина и креатинина у урину. Јачина гломеруларне филтрације (ЈГФ) израчуната је коришћењем формуле *Modification of Diet in Renal Disease*. Дужина бубрега и дебљина паренхима измерени су ултразвуком.

Резултати Концентрације глукозе у серуму наште (12,0 ± 2,79 *vs*. 9,50 ± 2,22, $p < 0,001$) и *HbA1c* (7,99 ± 1,43 *vs*. 7,49 ± 1,29, $p < 0,031$) смањивале су се током три године. Албуминурија се повећала (43,75 ± 10,83 *vs*. 144,44 ± 52,70 *mg/l*, $p < 0,001$) и ЈГФ се значајно смањила (63 *vs*. 58,3 *ml/min*/1,73 m^2) током студије, док је концентрација липида у серуму остала непромењена. Средња дужина бубрега и дебљина паренхима смањиле су се током три године. Линеарном регресионом анализом утврђено је да су систолни крвни притисак, гликемија наште, *HbA1c* позитивни, а дужина бубрега и дебљина паренхима негативни предиктори повећања протеинурије, док је протеинурија издвојена као негативан, а концентрација гвожђа и албумина у серуму као позитивни предиктор годишње промене ЈГФ.

Закључак Висок крвни притисак и висок *HbA1c* издвојени су као значајни фактори ризика за повећање протеинурије, која је значајан предиктор смањења ЈГФ код болесника са ДН.

Кључне речи: дијабетесна нефропатија; прогресија; фактори ризика

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparative analysis of effects of three different doses of fentanyl and standard dose of bupivacaine on a spinal block in patients with hip endoprosthesis surgery

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SUMMARY

Introduction/Objective Spinal anesthesia is often used for hip endoprosthesis surgery. Significant surgical stress response consisting of hormonal, metabolic and inflammatory changes can be initiated by the hip replacement surgery. Intrathecal opioids, as adjuvants to local anesthetics, make spinal block sufficient even with lower doses of the local anesthetics, and the incidence of the side effects reduce to minimum.

Methods This study included 162 patients of either sex, American Society of Anesthesiology classification (ASA) 1–2, scheduled for total hip arthroplasty. The patients had spinal anesthesia with 10 mg of 0.5% bupivacaine with 20 μg (Group I), or 25 μg (Group II) or 30 μg fentanyl intrathecally (Group III).

Results Mean time to achieve maximum motor and sensory blockade was with no significant difference among the groups. Time of motor block duration was shorter in the Group III. Four hours after the operation, patients in the Group I had significantly higher cortisol serum levels. Blood glucose levels were with no significant difference among the groups. Levels of CRP increased remarkably postoperatively in the Group I. Incidence of hypotension, bradycardia, nausea and vomiting was significantly higher in the Group III. Pruritus and shevering were not recorded among the groups. The first time an analgetic was needed postoperatively was the longest in the Group III.

Conclusion The dose of 10 mg of bupivacaine combined with 25 μg fentanyl was the optimal option to achieve hemodynamic stability, sufficient sensory and motor blockade, and reduce the stress response and incidence of the opioids side effects such as vomiting, nausea, pruritus etc.

Keywords: spinal anesthesia; bupivacaine; fentanyl; postoperative analgesia

INTRODUCTION

Significant surgical stress response consisting of hormonal, metabolic and inflammatory changes can be initiated by the hip replacement surgery [1, 2]. The controlled trauma of a surgical insult activates the afferent nerve signals from the surgical site and stimulates the production of corticotrophin-releasing hormone and arginine vasopressin. These peptides stimulate secretion of adrenocorticotropic hormone which stimulates cortisol secretion [3]. The effects of cortisol in the setting of surgical stress include suppression of insulin and mobilization of energy stores, increased proteolysis, sodium and water retention leading to preservation of blood pressure, suppression of the immune inflammatory response and delayed wound healing through its effects on collagen synthesis. Cortisol enables the synthesis and release of catecholamines and contributes to normal vascular permeability, vascular tone, and myocardial contraction by regulating β-receptor synthesis and regulation [4, 5].

Spinal anesthesia is often used for hip endoprosthesis surgery. During a spinal anesthesia there are many side effects as a result of sympathetic nervous system blockade. Post spinal anesthesia hypotension is caused by the decrease in the sympathetic outflow causing arterial vasodilatation, a decrease in venous return and consequently the activation of the Bezold–Jarisch reflex that elicits a triad of bradycardia, vasodilatation and further hypotension [6]. The incidence of hypotension during the spinal anesthesia is about 16–33% [7]. Compensatory mechanisms are generally more effective in young patients [8]. In elderly patients there are reduced physiological reserve and associated comorbidities [9]. Acute hypotension reduces cerebral perfusion, which leads to transient ischemia and activates the vomiting center [10]. To reduce the incidence and severity of hypotension, various strategies have been developed: preloading/co-loading fluids, use of vasoconstrictors and low doses of local anesthetics [11, 12].

Spinal anesthesia can provide good perioperative pain control. The pre-surgery block contributes to intra-operative analgesia and reduces the need for other analgesics [13].

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The use of the lower doses of local anesthetics combined with opioids, while providing a spinal block, may result in a better hemodynamic response of the patients and minimal incidence of the side effects [14, 15]. Besides analgesia, this anesthetic technique protects patients by reducing the immune response and the incidence of the postoperative complications.

The aim of this study is to compare the efficiency of three different intrathecal doses of fentanyl (20 μg, 25 μg and 30 μg) added to standard dose of local anesthetic (2 mg 0.5% bupivacaine) during the elective hip replacement surgery. The efficiency of the opioid used refers to less surgical stress, less side effects and longer duration of analgesia.

METHODS

All procedures performed in the study involving human participants were done in accordance with the ethical standards of the Helsinki declaration and its later amendments. Furthermore, the research was approved by the Ethics Committee of the Faculty of Medicine of the University of Niš on September 12, 2017; ref. N_0.: 12-8765/ 8. Informed consent was obtained from all individual participants included in the study.

This study included 162 patients of either sex, American Society of Anesthesiology physical status classification 1–2, scheduled for total hip arthroplasty. All patients had surgical treatment in the morning. The patients were randomized into three groups:

Group I: Patients that received 10 mg (2 ml) 0.5% bupivacaine and 20 μg (0.4 ml) of fentanyl intrathecal;

Group II: Patients that received 10 mg (2 ml) 0.5% bupivacaine and 25 μg (0.5 ml) of fentanyl intrathecal;

Group III: Patients received 10 mg (2 ml) 0.5% bupivacaine and 30 μg (0.6 ml) of fentanyl intrathecal.

Sensory blockade was evaluated by the bilateral pinprick method. Motor blockade was evaluated by the modified Broomage test (0 – without paralysis; 1 – unable to lift extended legs; 2 – unable to flex knee; 3 – unable to flex feet or complete motor blockade).

Serum levels of cortisol, glucose and C-reactive protein (CRP) were measured in all groups preoperatively and four, 12, and 24 hours after surgery.

The cardiovascular status of the patients was monitored by non-invasive methods such as: ECG monitoring, systolic, diastolic and mean arterial pressure, in five-minute intervals.

The side effects on the central nervous system and gastrointestinal system such as: shivering, nausea, vomiting, and pruritus were followed up and recorded intra-operatively or postoperatively.

The intensity of pain was assessed in the 30th, 60th, 90th, 120th, 180th, 240th, and 300th minute after the anesthesia was given in two ways:

– visual analog scale (0 – without pain to 10 – the worst pain);
– numerical scale (0 – without pain to 10 – the worst pain).

Duration of sensory blockade and the first time an analgesic drug was needed postoperatively were also recorded.

RESULTS

There was no statistically significant difference regarding ages, body mass index and the duration of surgery in all groups ($p < 0.05$) (Table 1).

Table 1. Patient characteristics

Group (number of patients)	Age (years)	Sex (M/F)	BMI (kg/m^2)	Duration of surgery (min)
I (n = 54)	69.1 ± 8	30/24	25.5 ± 3.1	104.4 ± 9.6
II (n = 54)	66.6 ± 7.5	38/16	24.3 ±3.8	106.9 ± 8.6
III (n = 54)	67.5 ± 7.7	34/20	24.4 ± 3.4	105.6 ± 8.6

There was no statistically significant difference regarding age, body mass index (BMI) and the duration of surgery in all the groups ($p < 0.05$)

There was no significant difference between the groups' mean time to achieve maximum motor blockade. The time of motor blockade duration was significantly shorter in Group II ($p < 0.05$) (Table 2).

Table 2. Motor blockade characteristics

Group	Time to achieve motor blockade I (min)	Time to achieve motor blockade II (min)	Time to achieve motor blockade III (min)	Time to achieve motor blockade IV (min)	Time duration of motor blockade (min)
I	2.2 ± 0.6	3.2 ± 0.8	4 ± 1	4.7 ± 1	166.0 ± 7.8
II	2.4 ± 0.7	3.4 ± 0.7	4.5 ± 0.6	4.6 ± 0.6	141.7 ±15.3
III	2.1 ± 0.6	3 ± 0.7	3.9 ± 0.7	5 ± 0.6	128.7± 15.1

Mean time to achieve maximum motor blockade was with no significant difference among the groups; the time of motor blockade duration was significantly shorter in Group II ($p < 0.05$)

The mean time to achieve maximum sensory blockade was comparable among the three groups ($p < 0.05$) (Table 3). It was with no significant difference among the groups.

Table 3. Characteristics of sensory blockade

Group	Time for distribution of sensory blockade until T10 (min)	Time to achieve maximal sensory blockade (min)
I	4.3 ± 0.5	6.4 ± 0.4
II	4.4 ± 0.8	6.6 ± 0.7
III	4 ± 0.7	6.2 ± 0.9

Mean time to achieve maximum sensory blockade was with no significant difference among the groups ($p < 0.05$)

At the fourth, 12th and 24th postoperative hour, the hormones of the surgical stress response were recorded. The study showed that patients in Group I had significantly higher cortisol serum levels at the fourth hour after surgery (Table 4).

Blood glucose levels were not significantly different among the groups. Levels of CRP increased remarkably postoperatively in the Group I (Table 5).

Table 4. Average serum cortisol levels (nmol/l) in the groups with 20 μg, 25 μg, and 30 μg intrathecal fentanyl, four, 12, and 24 hours postoperatively

Group	Preoperatively (nmol/l)	Postoperatively (nmol/l)		
		4 hours	12 hours	24 hours
I	472.4 ± 167.6	593.2 ± 277.3	850 ± 265.1	698 ± 105.3
II	692.6 ± 219.7	636.7 ± 184.2	789 ± 278.2	490.3 ± 170.6
III	558.5 ± 353.1	441.8 ± 249.4	765 ± 149.4	441.6 ± 277.3

Patients in Group I had significantly higher cortisol serum levels at the fourth hour after the surgery ($p < 0.05$)

Table 5. Levels of C-reactive protein (mg/L) four, 12, and 24 hours postoperatively

Group	Preoperatively (mg/L)	Postoperatively (mg/L)		
		4 hours	12 hours	24 hours
I	18.9 ± 3	108.4 ± 1.1	78.7 ± 26.6	65.3 ± 28.9
II	5.9 ± 2.2	5.3 ± 1.7	21.3 ± 11.2	11.2 ± 8.9
III	16.1 ± 2.5	18.7 ± 1.6	56.8 ± 15.6	44.9 ± 21.4

Levels of C-reactive protein increased remarkably postoperatively in Group I ($p < 0.05$).

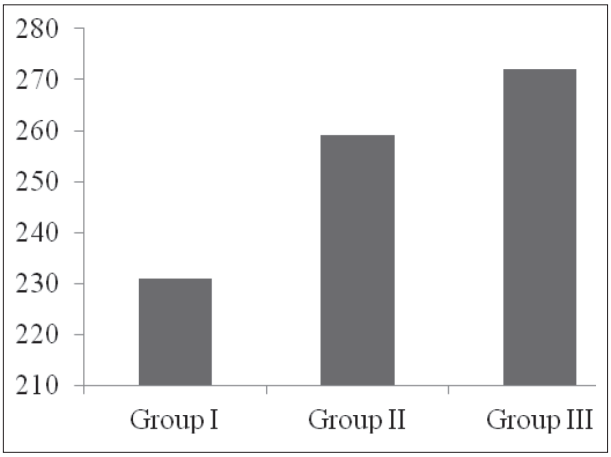

Figure 1. New analgesic needed postoperatively; the longest time until new analgesic was needed postoperatively was in the Group III ($p < 0.05$).

Table 6. Prevalence of side effects

Group	Hypotension		Bradycardia		Nausea		Vomiting	
	Number of patients (n)	%	Number of patients (n)	%	Number of patients (n)	%	Number of patients (n)	%
I	17	31.5	11	20.4	0	0	0	0
II	18	33.3	13	24.1	2	3.1	0	0
III	25	46.3	18	33.3	4	7.4	2	3.7

Incidence of hypotension, bradycardia, nausea and vomiting were significantly higher in Group III ($p < 0.05$).

Incidence of hypotension, bradycardia, nausea and vomiting were significantly higher in Group III ($p < 0.05$) (Table 6). Pruritus and shivering were not recorded among the groups.

The longest time until new analgetic was needed postoperatively was in the Group III (Figure 1).

DISCUSSION

The intensity of sympathetic nervous system blockade depends on the local anesthetic dosage. A degree of sympathetic blockade and consequent hypotension after spinal anesthesia can be reduced by using small doses of local anesthetic. On the other side, a more breakthrough pain was reported with bupivacaine doses of 5 mg or less [16]. This tendency to adopt a higher dose approach is likely to be attributable to concerns that duration of spinal anesthesia may not be sufficient for the proposed surgery when bupivacaine < 10 mg is used [17].

The success of spinal anesthesia with low dose of local anesthetic can be improved by addition of opioids. Intrathecally fentanyl doses not make additional effects on the sympathetic blockade, but makes duration of analgesia longer [18, 19].

In this study, the maximum dose of the intrathecal solution of 0.5% bupivacaine was 2 ml (10 mg) with 30 μg (0.6 ml) fentanyl. This dose was defined by the results of the previous studies [19, 20]. Lower doses of local anesthetics combined with opioids may result in inadequate sensory or motor blockade. Intra-operatively, analgesia was adequate in all groups. Similar results had Ben et al. [20] with intrathecal dose of 4 mg bupivacaine with 20 μg fentanyl.

Bibhush [21] compared three different doses (12.5 mg, 10 mg and 5 mg) of 0.5% bupivacaine, with 25 μg fentanyl. The results of this study showed that the dose of 5 mg of bupivacaine in combination with 25μg of fentanyl intrathecally had inadequate motor blockade, while the dose of 10 mg of bupivacaine increased intensity and duration of both, sensory and motor blockade. The time was 241.96 minutes. In this study the duration of motor blockade was 141.67 ± 15.3 minutes.

In this study, increasing the dose of fentanyl from 0.4 ml (20 μg) to 0.5 ml (25 μg) and 0.6 ml (30 μg) resulted in the increase of the maximum level of sensory blockade. The time of achieving maximum analgesia was with no significant difference among the groups. Kuusniemi [22] had similar results.

Cortisol has been researched in order to find the best anesthetic approach to reduced surgical stress response. Opioids, fentanyl and morphine, can reduce surgical stress response. Kwon et al. [23] hypothesized that circadian rhythm of cortisol might affect postoperative cortisol levels depending on the surgery start time. Cortisol recovery to preoperative level was faster in the afternoon surgery than in the morning surgery group. In this study, all patients had surgical treatment in the morning. Postoperative cortisol increased, similar to previous studies, except in the Group II, where the values were the same as before surgery. Cortisol serum level was significantly higher in the Group I at the fourth postoperative hour. Postoperatively, at 12th hour, there was a remarkable increase of the cortisol serum levels in all groups.

CRP serum levels were without any significant differences among the groups. At the fourth postoperative hour, the level of serum CRP was significantly higher in the Group I. Even after 12 hours it showed higher levels.

Impaired metabolism of glucose has influence on wound infection, and can cause cardiac and thromboembolic complications. Hahn et al. [24] mention the reduction of the postoperative complications in patients who were not diabetics. Glucose blood level is very important peri-operatively and postoperatively. In this study, blood glucose levels were not significantly different among the groups.

As a result, Knigin et al. [25] described spinal hypotension in 43.4% of patients. Rao et al. [26] described hypotension in seven out of 30 patients in a group with 8 mg bupivacaine combined with 25 μg fentanyl. Malhotra et al. [27] reported that the highest incidence of hypotension had a group with 12.5 mg of bupivacaine combined with 25 μg fentanyl. In this study, hypotension was described in 60 patients (37%). In Group I it was described in 17 (31.5%) patients. In Group II hypotension was described in 18 (33.3%) patients, and in Group III in 25 (46.3%). Better hemodynamic stability was observed in patients with 10 mg bupivacaine and 20 μg fentanyl. Ali et al. [28] reported pruritus with higher doses of fentanyl (25 μg). Akanmu et al. [29] described pruritus and shivering only in patients who received 10 mg of bupivacaine with 25 μg of fentanyl. Pruritus and shivering were not recorded among the groups in our study.

In our study, the longest time of analgesia was observed in the Group III, 272 ± 21 min. Akanmu et al. [29] found that analgesia lasted the longest in patients who received 10 mg of bupivacaine with 25 μg of fentanyl, and it was 276.23 ± 26.21 min.

CONCLUSION

Spinal anesthesia using standard doses of local anesthetics for hip endoprosthesis surgery in geriatric population, often causes hemodynamic instability due to reduced physiological reserve and comorbidities of patients. In order to prevent negative side effects and complications, but achieve an appropriate sensory and motor blockade, the use of lower doses of local anesthetics combined with opioids was implemented in practice.

The dose of 10 mg (2 ml) of bupivacaine combined with 25 μg (0.5 ml) fentanyl, in this study, was the optimal option to achieve hemodynamic stability, sufficient sensory and motor blockade, and reduce the stress response and the incidence of the opioids side effects such as vomiting, nausea, pruritus, etc.

Conflict of interest: None declared.

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Компаративна анализа три различите дозе фентанила у комбинацији са стандардном дозом бупивакаина код спиналног блока код болесника подвргнутих елективној операцији уградње вештачког кука

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САЖЕТАК

Увод/Циљ Спинална анестезија честа је анестезиолошка техника која се користи током хируршке интервенције уградње вештачког кука. Овај хируршки третман може изазвати системски одговор на хируршки стрес, односно хормонске, метаболичке и запаљенске промене. Интратекално дати опиоиди као адјувант локалног анестетика остварују синергистички ефекат са њим чинећи спинални блок потпунијим чак и при примени нижих доза локалног анестетика, а инциденцу нежељених ефеката своде на минимум.

Методе Студијом су обухваћена 162 болесника, оба пола, из групе 1–2 по класификацији *ASA* (Америчког друштва анестезиолога), подељена у три групе методом случајног избора. Испитаници су добијали 10 *mg* 0,5% раствора бупивакаина и 20 *μg* (Група I) или 25 *μg* (Група II) или 30 *μg* (Група III) фентанила интратекално.

Резултати Није било статистички значајне разлике у времену потребном за постизање потпуне моторне и сензитивне блокаде међу групама, док је време трајања моторне блокаде било знатно краће у Групи III. Постоперативно, током прва четири сата болесници Групе I имали су највећу вредност кортизола у серуму. Ниво гликемије у крви није имао статистички значајну промену вредности. Током постоперативног периода вредности *CRP* биле су највише код болесника Групе I. Инциденца хипотензије, брадикардије, мучнине и повраћања била је највећа у Групи III. Свраб и дрхтање нису описани ни у једној од испитаних група. Постоперативно, најдужи период до потребе за аналгетиком описан је код болесника Групе III.

Закључак Применом 25 *μg* фентанила, као адјуванта локалном анестетику, 10 *mg* 0,5% бупивакаину, постиже се адекватна хемодинамска стабилност, моторна и сензитивна блокада, смањује одговор организма на хируршки стрес и редукује инциденца нежељених ефеката опиоида, мучнина, повраћање, свраб итд.

Кључне речи: спинална анестезија; бупивакаин; фентанил; постоперативна аналгезија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The laparoscopic repair of inguinal hernia in female children in the Republic of North Macedonia

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SUMMARY

Introduction/Objective Laparoscopic inguinal hernia repair in children is a minimally invasive method, and with its safety, feasibility, and excellent cosmesis is an acceptable alternative to open repair.

Methods This is a prospective clinical study, with national data of 49 female children aged 1–14 years, treated via laparoscopic approach. Operative time, time to verticalization (normal position in bed, standing/walking), hospital stay, nausea, pain, and cosmetic effects (size and visibility of the mark) were elaborated.

Results The results revealed that five (10.2%) children had a family history of inguinal hernia. A total of 29 (59.2%) children had hernia located on the right side, 19 (38.8%) on the left side, and one (2%) on both sides. The average diameter of the inguinal opening was 3 ± 2.17 cm. Sixteen children (32.7%) had hidden hernia. The average operation time of the unilateral intervention was 29.5 ± 6.8 minutes, and for bilateral hernias it was 43.6 ± 7.2 minutes. The average length of hospitalization was 14.1 ± 3.1 hours, and the time needed for a full return to a normal position in bed was 2.6 ± 0.6 hours. The average length of the scar in both the right and the left groin region was 2.2 ± 0.4 mm. A total of 46 (93.9%) parents/guardians were satisfied by the esthetic result, while three (6.1%) had no particular opinion regarding this question.

Conclusion The introduction of laparoscopic surgery in the treatment of inguinal hernia is a promising method, which plays an important role as an alternative surgical technique because of the minimal invasiveness of the technique and improved recovery of the children.

Keywords: children's inguinal hernia; PIRS – percutaneous internal ring suturing; minimally invasive surgery

INTRODUCTION

Inguinal hernia is far more common in males [1, 2, 3]. Available data suggest that the overall incidence of inguinal hernias in childhood ranges 0.8–4.4% (to more than 30% in infants born preterm), with the incidence in boys being 10 times higher compared to girls. Similarly, a study of almost 80,000 children in the USA showed that the cumulative incidence of inguinal hernia from birth to the age of 15 was 6.62% in males and 0.74% in females [4, 5].

Surgery is required for almost all pediatric patients with inguinal hernia. Unlike hernias in adults, hernias in children are treated when they are diagnosed, even if they are asymptomatic. It is the most common surgical procedure in children that makes up more than 95% of treatments of all hernias [6, 7]. Operation prevents the occurrence of complications, such as incarceration and obstruction, which may potentially result in ischemia and necrosis of the hernia content. In comparison with boys, girls with inguinal hernia, whose content are ovaries and Fallopian tubes, are at risk of compression or torsion of the gonadal structures, which leads to ovarian ischemic stroke [8].

The golden standard for treatment of inguinal hernia is open herniotomy and herniorrhaphy, a procedure with a high rate of success and a relatively low rate of complications [6]. Still, inguinal hernia treatment has achieved great advancements over the centuries [6]. The introduction of laparoscopic surgical treatment for inguinal hernia, first performed in 1993 and 1994, seems to play a significant role in terms of safety, visibility, as well as simultaneous treatment of the contralateral side, and a better esthetic result [9].

The trend has been turned towards the application of laparoscopic techniques with a rapid movement forward and a number of different laparoscopic techniques, an upward trend of the use of extracorporeal knotting and a decrease of the use of working ports and endoscopic instruments, as alternatives to open surgery [10–16].

The laparoscopically assisted technique of percutaneous internal ring suturing with one port, was initially introduced by Patkowski in 2004, as a minimally invasive method with a high success rate and rare complications [17].

It seems that among numerous techniques for treatment of inguinal hernias during childhood in the last decade, the one-port laparoscopic technique of internal ring suturing represents a very competitive achievement regarding this issue [18, 19].

The aim of this study was to present the national experience of the Republic of North

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Macedonia in laparoscopic (percutaneous internal ring suturing – PIRS) repair of inguinal hernia in female children.

METHODS

The analysis represents a prospective clinical study, which has elaborated national data of 49 female children 1–14 years old, with clinically diagnosed indirect inguinal hernia treated by laparoscopic PIRS. The study was carried out at the University Clinic for Pediatric Surgery, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia – as the single national center for laparoscopic (PIRS) repair. We started to implement this technique during 2015, as the only institution where the PIRS treatment of clinically diagnosed indirect inguinal hernia of female children was performed.

The PIRS method we used had been introduced by Patkowski and involves the percutaneous closure of the internal inguinal ring under the control of a telescope placed in the umbilicus. The telescope was used to control all procedures, with optics of 5 mm, and an angle of view of 30°.

The insufflation pressure in the peritoneal cavity was maintained at 8–10 mmHg. The internal ring of the inguinal canal was closed using non-absorbable 2-0 monofilament sutures. The wound in the umbilicus was closed using absorbable 3-0 sutures, and the skin was closed with non-absorbable 4-0 or 5-0 monofilament sutures. The patient condition allowed discharge on the first postoperative day.

The study covered all national cases of interest during the period between 2015 and 2017. We elaborated the operative time, time to verticalization (normal position in bed, standing/walking), hospital stay, nausea, pain and cosmetic effects (size and visibility of mark). All the children were asked for outpatient follow-up examination on the seventh day and three months after the laparoscopic surgery. At the time of the second follow-up visit, the parents were asked of symptoms, such as recurrent hernia, swelling or lump in the groin, local pain, palpable stitches in the groin area, and their personal opinion on the appearance of the scar and whether, if necessary, they would choose this treatment again or recommend it to others.

The study was approved by the Ethics Committees of the University Clinic of Pediatric Surgery and Faculty of Medicine of the Ss. Cyril and Methodius University of Skopje. Written consents from parents/guardians were obtained according to the Declaration of Helsinki and local ethics committees.

RESULTS

The study presents national data of 49 female children with clinically diagnosed indirect inguinal hernia. All of them aged 1–14 year [mean age 5.3 ± 2.7 with Median IQR = 5 (3–7)] and were treated via PIRS during the three-year period (2015–2017).

Characteristics of inguinal hernia

Five (10.2%) children had a family history of inguinal hernia. A total of 29 (59.2%) children had hernia located on the right side, 19 (38.8%) had it on the left side, and one (2%) had it on both sides. About 22 (44.9%) children had hernia for a duration of one to two years, followed by 11 (22.4%), where the duration was 6–12 months, eight (16.3%) with a duration of two to five years, and three (6.1%) with a duration of more than five years. None of the females had hernia with a duration of less than 1 month.

Pre-operative symptoms

About 32 (65.3%) children felt discomfort, nine (18.4%) experienced pain, and 43 (87.8%) had swelling. The average number of existent pre-operative symptoms in children was 2.1 ± 0.7, with one to four symptoms.

Intervention

The length of the inguinal opening was 3 ± 2.17 cm, with a minimum of 2 cm and a maximum of 5 cm. During the intervention, two (4.1%) cases had conversion in the open technique. In 16 (32.7%) children, the presence of hidden hernia was found, 50% of them on the left side and 50% on the right side, all surgically treated during the same intervention. The average length of the unilateral intervention was 29.5 ± 6.8 minutes, with min/max. time of 15/45 minutes. In bilateral hernias, the average length of the intervention was 43.6 ± 7.2 minutes, with min/max. time of the intervention of 25/55 minutes, and the length of the intervention was less than 45 minutes in 50% of the female patients.

Hospitalization

The average length of hospitalization was 14.1 ± 3.1 hours, with min/max. time of hospitalization of 10/24 hours, and the length of the postoperative stay in hospital was less than 12 hours in 50% of female patients.

Return to normal activities

The time needed for a full return to a normal position in bed was 2.6 ± 0.6 hours, with a min/max. time of 2/4 hours, and the time was shorter than three hours in 50% of the patients. The time to verticalization was 3.6 ± 0.8 hours, with a minimum of two and a maximum of six hours. In 50% of the females this time was shorter than four hours.

Postoperative discomfort

None of the females had postoperative nausea. The average grade of pain according to the VAS scale of 0–10 was 0.3 ± 0.5, with a min/max. of 0/2. No pain was registered in 50% of the patients. Analgesic therapy with one dose was given to four (8.2%) children.

Esthetics

The average length of the scar was 2.2 ± 0.4 mm, with min/max. length of 2/3 mm and the scar was smaller than 2 mm in 50% of the patients for median IQR = 2 (2-2). Esthetics was an important issue for 37 (75.5%) parents/guardians. In our case, 38 (77.5%) parents/guardians thought that the mark did not disrupt the esthetics, while 11 (22.5%) were undetermined. About 46 (93.9%) parents/guardians felt that they would recommend this intervention to others who have children with inguinal hernia.

DISCUSSION

Throughout history, many concepts of surgical treatments of hernia have changed and been applied by pediatric surgeons in their everyday practice [6]. The last decade marks an evolution in techniques, from three-port to two-port and one-port laparoscopic technique [9–13].

Intracorporeal suturing and knotting are becoming unpopular among pediatric surgeons according to the results of various studies. Intraabdominal skills are necessary, such as intracorporeal suturing, knotting and needle handling, which in essence take up a lot of time in context of the time needed to carry out the procedure [16].

At the beginning, the laparoscopic treatment often lasted longer than the open technique treatment. However, once the learning curve was passed, the duration gradually decreased [16]. Researchers have shown that the operating time was in an interval of 20–74 minutes [17]. Patkowski on the sample of 140 hernias discovered that the average PIRS operative time for unilateral hernias was 19 minutes, while it was 24 minutes for bilateral ones [17].

Wolak and Patkowski reported the average PIRS time of 31.6 minutes for bilateral, and 28.2 (15–45) minutes for unilateral hernias [19]. For Lipskar, the average operative time was 37 ± 10 minutes [20]. The average length of the unilateral intervention in our study was 29.5 ± 6.8 minutes, with min/max. time of 15/45 minutes. In bilateral hernias, the average length of the intervention was 43.6 ± 7.2 minutes, with min/max. time of the intervention being 25/55 minutes.

With the conventional open surgical techniques, patients have a relatively larger skin incision, while in other laparoscopic treatments three or four skin incisions are necessary for inserting the trocars. The PIRS technique can be carried out with only one incision, concealed in the bellybutton region and extracorporeal suture. In comparison to open surgery, laparoscopic hernioplasty offers excellent visual exposition, minimal dissection and reduced trauma of the surrounding tissue. It offers the opportunity to identify unexpected conditions, such as direct or femoral hernia, as well as other intraabdominal processes and pathologies (intersexual anomalies) and other conditions [13–16].

Chan discovered that children after the laparoscopic treatment of inguinal hernia had less pain and had made faster recovery, which is similar to our results [21]. We found that none of the children had postoperative nausea, and for full return to a normal position in bed as well as standing/walking, the time was 2.6 vs. 3.6 hours.

One of the advantages of laparoscopic hernioplasty is the possibility of exploration of the contralateral side, which in fact means higher costs and distress to the child and their parents. Around 38–100% of children with unilateral inguinal hernia have contralateral open patent processus vaginalis (PPV) [22]. In 60% of children with unilateral hernia, contralateral PPV is present at two years of age, in 40% it is present for those over two years of age, while half of these children are at risk and can develop inguinal hernia. There is a risk of about 10% of developing hernia, if the hernia from the left is primarily treated.

However, Li et al. [23] reported a rate of development of metachronous hernia of 5.2%. It is believed that the sex of the child, girls opposed to boys, has a slight influence on the incidence of metachronous hernia (6.05% in boys in contrast to 6.59% in girls; r = 0.202) [24, 25]. In our research, we found contralateral PPV in 32.7% – 4 on the left and 4 on the right side, all treated during the same intervention. With contralateral exploration and suturing of the asymptomatic inner inguinal ring, the manifested contralateral inguinal hernia can be prevented, and the need for additional surgery later in the child's life is eliminated.

As the PIRS technique has been offering excellent esthetic results, the majority of parents are satisfied with the use of this method for their children and recommend it to other parents whose children need to undergo surgery of this type.

Bharathi et al. [26] reported scars of 5 mm in PIRS treatment, Patkowski et al. reported nearly no visible scars, and Chan et al. stressed the superiority of the laparoscopic technique as one with an excellent esthetic effect [17, 27]. In a retrospective study by Amano et al. [28], from 1033 children with laparoscopic hernioplasty, on a 1–5 scale of satisfaction (5 being the highest), regarding the visibility of the scar, the results were 4.9 ± 0.5 points. In our study, 77.5% of the parents/guardians thought that the mark did not disrupt the esthetics and 93.9% of them were satisfied by the esthetic look.

According to the existent literature to date, there is no tool that would enable a view to the inside with a representation of the inner inguinal ring after its suturing. It is unknown whether the suturing of the inner inguinal ring keeps the inner ring closed for the remainder of the patient's life, or whether some kind of fibrosis or reorganization of the peritoneum would contribute to that. Although there are data in the literature concerning recurrent laparoscopy in patients with previous laparoscopic hernioplasty, the sample of patients is simply too small to come to a conclusion [21, 22, 24]. Still, the lack of noted complications makes this technique efficient and especially promising in girls [24].

CONCLUSION

The introduction of laparoscopic surgery in the treatment of inguinal hernia is a promising method, which plays an

important role as an alternative surgical technique, while at the same time it represents a diagnostic tool for exploration and simultaneous treatment of the contralateral inguinal ring. We found that this technique allows better recovery, quick return to full activity, and no visible scars. Most parents were satisfied with the treatment of their children by this method and would recommend it to others.

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Лапароскопска операција ингвиналне херније код женске деце у Републици Северној Македонији

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САЖЕТАК

Увод/Циљ Лапароскопска техника решавања ингвиналне киле код деце је минимално инвазивна метода, са великом сигурношћу, изводљивошћу и одличним козметским резултатом и прихватљива је алтернатива стандардној отвореној процедури.

Методе Ово је проспективна клиничка студија, са националним подацима о 49 девојчица узраста од једне до 14 година оперисаних лапароскопским приступом. Анализирани су оперативно време, време до вертикализације (нормалан положај у кревету, стајање/ходање), боравак у болници, мучнина, бол и козметски ефекти (величина и видљивост ожиљка).

Резултати Породичну анамнезу о постојању ингвиналне киле имало је петоро (10,2%) деце. Килу локализовану на десној страни имало је 29 (59,2%) болесника, на левој страни 19 (38,8%) болесника, а обострано ју је имао један болесник (2%). Просечан дијаметар ингвиналног отвора износио је 3 ± 2,17 *cm*. Шеснаесторо деце (32,7%) имало је скривену килу. Просечна дужина једностране интервенције била је 29,5 ± 6,8 минута, а билатералне киле 43,6 ± 7,2 минута. Просечна дужина хоспитализације била је 14,1 ± 3,1 сат, а време потребно за пуни повратак у нормалан положај у кревету било је 2,6 ± 0,6 сати. Просечна дужина ожиљка после операције била је 2,2 ± 0,4 *mm*. Четрдесет шест (93,9%) родитеља/старатеља били су задовољни естетским изгледом, а без посебног мишљења о овом питању била су три (6,1%) родитеља.

Закључак Увођење лапароскопске хирургије у лечење ингвиналне киле је обећавајућа метода, која игра важну улогу као алтернативна хируршка техника, због минималне инвазивности технике и бољег опоравка деце.

Кључне речи: дечја ингвинална кила; перкутано ушивање унутрашњег прстена; минимално инвазивна хирургија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Hand injuries in children and adolescents

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SUMMARY

Introduction/Objective The objective of the study was to determinate which groups in the population of children are most prone to hand injuries and to identify the causes of the injuries with the aim of further developing better means of severe injuries prevention that can lead to invalidity.

Methods A retrospective epidemiological study was carried out, and included all children with hand injuries admitted to our hospital between January 1, 2010 and December 31, 2017; The data were collected and analyzed statistically using SPSS®. Significance was defined as $p < 0.05$.

Results The total number of patients was 254, 202 boys and 52 girls, with a mean age for both sexes 10.13 years (range1–17). The majority of patients were from an urban population 56.7% and 43.3% were from a rural area. Regarding the month in the year when the injury occurred, there were two peaks, in January and in May. The right hand was more affected, 53.2%, than the left, 45.6%, and both hands were affected in 1.8% of cases. Isolated soft tissue injuries (skin, muscles, tendons) were present in 59% of cases, isolated bone injuries (phalangeal and metacarpal bone fractures) in 15.3%, and both soft tissue and bone injuries in 25.7% of cases. The little finger was the most affected, followed by the long finger and thumb, index and ring finger, respectively. The most serious injuries were from explosive wounds caused by firecrackers and handling agricultural tools and engines.

Conclusion Hand injuries in childhood are common and can have devastating consequences. Developing prevention program by raising awareness about this issue is of vital importance.

Keywords: hand injuries; children; adolescents; prevention

INTRODUCTION

Active children often injure themselves during everyday activities such as sports or playing with toys and with each other. They suffer lacerations, fractures, or crushing injuries of the hand, which can result in nerve, vessel and tendon lesions [1]. Injury is the cause of nearly 950,000 non-fatal hospitalizations among children each year worldwide, and the hand is the second most frequently injured region of the body among children [2, 3]. Almost 75% of all hand and finger injuries among children admitted to the emergency room are minor injuries; however, 25% are major injuries, most frequently fractures of the hand and the fingers. Furthermore, 15.5% of all the hand injuries had to be surgically treated [3]. The most significant are severe mutilated hand injuries, where an injured child faces physical limitations but also the experience of chronic pain and psychological issues, such as post-traumatic stress disorder. These types of injuries also have an impact on the children's parents, family and their community networks [2, 4]. Therefore, prevention of such injuries, if possible, should become a necessity.

The objective of this epidemiological study was to determine which groups in the population of children are most prone to hand injuries, and to identify the causes of injuries in the aim of further developing better means of prevention of severe injuries that can lead to invalidity.

METHODS

After institutional review board approval, medical documentation was retrospectively reviewed of all children with hand injuries admitted to our hospital between January 1, 2010 and December 31, 2017. The hospital itself is a tertiary level institution that covers a region of about two million people, and the only hospital within this region that treats hand injuries in children. Children with burn injuries and minor injuries treated in our outpatient clinic were excluded from the study. The following data were collected and entered into a Microsoft Excel® (Microsoft Office, Microsoft Corporation, Redmond, WA, USA) spreadsheet database: age, gender, place of residence, affected hands and fingers, and type of injury. The data were analyzed statistically using SPSS® version 23.0 (IBM Corp. Armonk, NY, USA), and mean, range, minimum, maximum values, and standard deviation (SD) were calculated. The variables were analyzed by a parametric Student's t test. Significance was defined as $p < 0.05$.

RESULTS

Over an eight-year period, the total number of patients was 254; there were 202 (79.5%) boys and 52 (20.5%) girls, with a mean age for both genders (mean = 10.13 years; SD = 5.16) and range of age (range 1–17 years; Min = 1;

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Max = 17). The student's t test showed a statistically significant difference (p = 0.002) in age between boys (mean = 10.58 years; SD = 5.20) and girls (mean = 8.38 years; SD = 4,65). Based on a division into different age groups, there were 65 patients in the 1–6 years age group, 77 patients in the 6–12 years age group, and 112 of adolescents in the 12–17 years age group with no statistically significant difference between the age groups (p > 0.05). The distribution of patients by age is presented in Figure 1.

The majority of patients were from an urban population 144 (56.69%) and 110 (43.3%) were from a rural area. Regarding the month of the year when the injury occurred, there were two peaks: in May, 29 injuries, and in January, 27 hand injuries, while the smallest number of injuries occurred in February, 13 (Figure 2).

The right hand was affected in 135 (53.2%) patients, the left in 116 (45.6%), and both hands in 3 (1.2%). The difference was not found to be statistically significant between the affected hand (left or right) between different age groups. Except for the hands, other regions of the body were affected in seven patients: the face in three, the abdomen in two, and the legs in two patients.

Isolated soft tissue injuries (skin, muscles, tendons) were present in 150 (59%) patients, isolated bone injuries (phalangeal and metacarpal bone fractures) in 39 (15.3%), and both soft tissue and bone injuries in 65 (25.7%) children with hand injuries. It should be pointed out that no carpal bone fractures were diagnosed. However, metacarpal bone fractures occurred in 30 patients, and in 23 only one metacarpal bone was fractured: the first metacarpal bone was affected in seven patients, the second in two, the third in one, the fourth in one, and the fifth was the most affected one in 12 patients. Multiple metacarpal fractures occurred in seven patients: fracture of all five metacarpal bones was found in only one child, four fractured metacarpal bones (II–V) were present in three patients, and fractures of both II and III metacarpal bones were found in three children. All metacarpal bone fractures were treated with cast immobilization, and in 19 patients, after closed or open reduction, fixation was performed with "K" wires. Due to the association of metacarpal bone fractures with extensor injury, tenorrhaphy was required in four patients.

Fingers were injured in 221 (87.07%) patients and the palm in 33 (12.92%). Injury of one finger only was present in 164, two fingers in 39, three fingers in 14, and four fingers in four patients. In this study, there were no children with an injury of all five fingers. The most affected finger was the little finger, 42, followed by the long finger and thumb, index and ring finger, respectively (Figure 3).

Sections of extensor and flexor tendons were present in 116 patients. In 31 they were associated with bone fractures, and in seven of those patients traumatic arthrotomy was present as well. Isolated sections of extensors occurred in 35, and in 25 patients an extensor section was associated with fractures. On the other hand, isolated injury of the flexor tendons was present in 50 patients, and bone fractures were associated only in three. In three patients both extensors and flexors were affected, accompanied with bone fractures. Sections of flexor tendons were associated

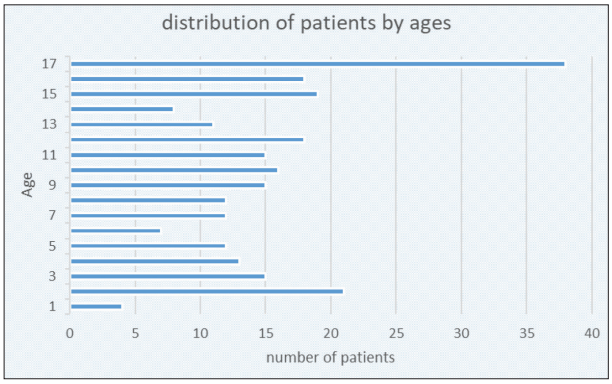

Figure 1. Representing a different incidence of hand injuries in age groups with the highest incidence in 17-year-olds

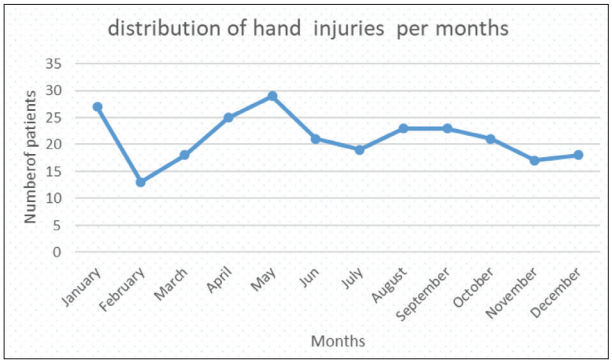

Figure 2. Graph presenting a bimodal distribution of hand injuries per months

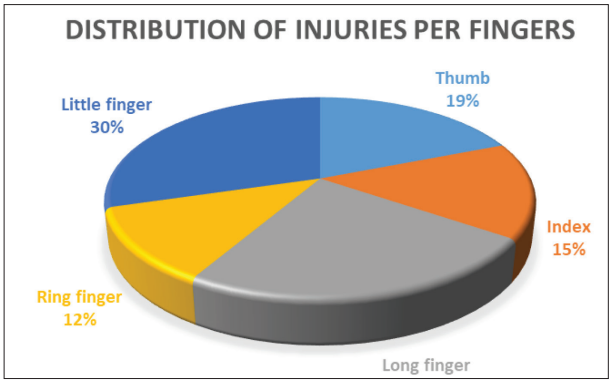

Figure 3. Representing number of injuries per each finger

with lesions of the median nerve in five and ulnar nerve in two patients; sections of the ulnar nerve associated with ulnar artery injury were present in two children. Repair was performed in all cases. Injury of the radial artery occurred in one patient with the section of flexor tendons of both hands, and ligation of the radial artery was performed.

Fracture stabilization with "K" wires was performed in 70, and cast immobilization in 176 patients. Stabilization with "K" wires was performed in all isolated bone fractures (39), but also in injuries that include bone fractures, traumatic arthrotomy, and extensor tendon ruptures. Cast immobilization was used in all cases which included bone fractures and both extensor and flexor tendon injuries.

Traumatic partial amputation was present in 39 patients (at the level of distal phalanges 36, middle phalanges one,

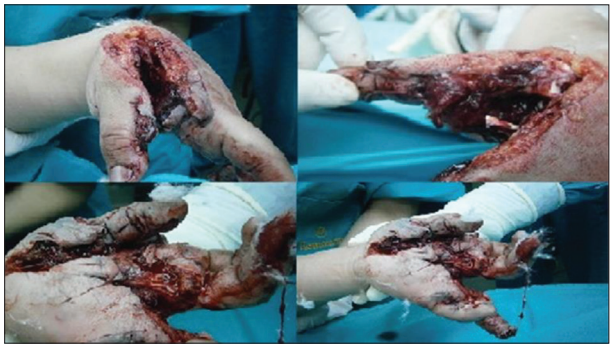

Figure 4. Initial finding of explosive wound in a 10-year-old boy

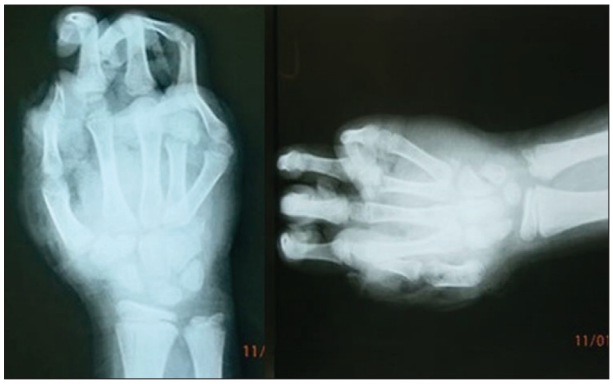

Figure 5. X-Ray of the injured hand

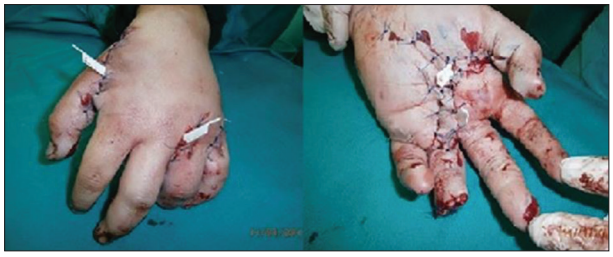

Figure 6. Appearance of the hand after reconstructive surgery was performed

and proximal phalanges two). Partial amputation of two fingers was present in six, and of three fingers in two patients. Fingertip partial amputations were caused by door slamming in 20 younger children, and in 15 were caused by different tools and machine handling among older children.

Traumatic amputation occurred in 21 patients (at the level of distal phalanges 15, middle phalanges four, and proximal phalanges 2). In five patients, traumatic amputation was present on three fingers (in four patients on the right hand, and in one on the left hand), and in one patient there was a traumatic amputation of the third and fourth fingers at the level of the proximal phalanges. These most serious injuries were caused by explosive wounds and handling of agricultural tools and engines (an ax, saw, circular saw, lawnmower, etc.). An explosive wound injury in a 10-year-old boy, including preoperative findings, X-ray and postoperative appearance, is presented in Figures 4, 5, and 6. In 15 patients, amputations were caused by handling of agricultural tools and machines, in four they were caused by explosive wounds, and in two by door slamming. Boys accounted for almost all of these amputations, except one which occurred in an eight-year-old girl and was caused by door slamming.

DISCUSSION

Bearing in mind that children are the most vulnerable population and that complex and massive hand injuries can result in lifelong disability, we carried out a study of hand injuries.

Our study showed that accidents cause soft tissue injuries of the fingers in most patients with or without bone fractures, resulting in temporary or permanent disability of the fingers. Injury prevention, and explaining mechanisms of injury during schooltime could be very important for the school-age population.

Ljungberg et al. [5] reported a male predominance of 61% in hand injured children, almost the same as Yorlets et al. [6] who reported a rate of 59% of males in their study. In our study, the percent of boys was much higher (79.5%) than that of girls (20.25%), with an accompanying significant difference in age (10.51 years for the boys compared to 7.84 years for the girls). Vadivelu et al. [7] published that the incidence of hand injury was low in toddlers (34/100,000), that it more than doubled in preschool children (73/100,000), and steeply increased after the age of 10 (663/100,000). The incidence increased with age in our analysis: it was 25.5% in the 1–6 age group, 30.3% in the 6–12 age group, and 44.2% in the oldest group, 12–17 years old.

Isolated bone injuries accounted for 15.3% of all injuries, and combined with soft tissue injuries such as tendon lesions, the number reached nearly 59%, which correlates with the findings in the study by Vadivelu et al. [7] of 65.5%. Fingertip injuries are the most common hand injuries among children with an incidence rate of 37–46% in the literature. Distal phalanx fractures in childhood are very common and mostly caused by slamming a child's finger in a door [5, 6, 8]. Door slamming was the cause of fingertip amputation and partial amputations in 57% of cases included in this analysis, while partial amputations and amputations at the level of distal phalanges occurred in 71.15% of the amputation/partial amputation hand injuries. Tendons of both flexors and extensors were injured in 45.6% of all patients. Injury of the flexors was associated with nerve lesions and extensors with traumatic arthrotomies and bone fractures. Extensors were more affected in this study, which correlates with the findings of Kim et al. [9], who also reported a higher incidence of extensor injury. Pediatric tendon injuries are no less severe than injuries in adults, and an excellent and good outcome could be achieved in 41% and 48% of the patients, respectively [9, 10].

The majority of injuries were caused by a simple fall or glass cuts; however, the most severe ones were caused by firecrackers and fireworks, or handling of agricultural tools and machines, which correlates with the highest incidence in January around New Year's Eve and in the spring months with the start of the agricultural season. Children's patterns of injury change with age, and priorities for injury

prevention alter according to stages of development [2]. Sandvall et al. [11] reported in their study that more rocket injuries were noted among children (44%), homemade firework injuries among teens (34%), and more shell/mortar injuries among adults (86%), while 37% of all hand-injured patients had at least one partial or whole finger/hand amputation. Although selling of any kind of fireworks and explosive items is strictly prohibited, these items are unfortunately sold illegally and 35.3% of finger amputations were caused by firecrackers, fireworks, and explosive.

Despite the fact that child labor is against the law in our country, in rural areas it is a practice among low-income families for children to help their parents with agricultural work, which is also the cause of numerous injuries that can lead to invalidity. In our study, 64.7% of finger amputations occurred in older children handling agricultural tools and machines. Youths and young adults who work in the agricultural sector experience high rates of injury, and risk of this type of injury relates directly to the amount and types of farm work exposure [12]. Children can sustain significant injuries with unsafe lawnmower use such as mutilating injuries of the foot, legs, hands, and arms. The ride-on mower injuries were more likely to involve amputations and longer hospitalization when compared to walk-behind mower injuries. Garay et al. [13] have published that at least 69% of accidents might have been prevented if children younger than six had not been near a lawnmower, and those younger than 12 had not been operating one [14]. Stögner et al. [15] have reported that ball sports, cycling, and equestrian sports were the predominant cause of their recorded hand injuries, mostly fractures, while Gesslein et al. [16] report a high incidence of acute hand and wrist injuries in elite taekwondo athletes despite the use of protective hand gear. Interestingly, in this study there were no hand fractures requiring surgical management among child athletes.

Orthopedic hand injuries in children are very demanding, bearing in mind that the growing skeleton poses a different diagnostic and therapeutic challenge than the mature skeleton, as its unossified cartilaginous sections are still more susceptible to injury than bone. Although remodeling can correct for even moderate deformities if sufficient growth potential exists, remodeling cannot return the child to normal anatomy in many cases [17]. Also, 30% of peripheral nerve injuries involve the hand which adds to the complexity of orthopedic management in this type of injury [18].

Most of the injuries were caused by accidents. Thus, the truth is that some of them could have been prevented. With the aim of providing protection against and preventing future injuries, our hospital has formed a team dedicated to working with abused and neglected children. When suspicion of abuse or neglect regarding a child arises, a questionnaire which includes 30 questions about the social-economic conditions of the child's environment and mechanism of injury is used. A social worker is actively involved in all suspicious cases. The role of the social worker is to interview parents, assess the circumstances under which the injury happened, exclude the possibility of alcohol or drug abuse in the family, and give them advice on how to prevent injuries in the future if the injuries were accidental. The social worker has a crucial role in linking a multidisciplinary team consisting of pediatric surgeons, psychologists, and lawyers in cases of non-accidental injuries. Kendrick et al. [19] reported that evidence-based resources for preventing thermal injuries, falls and scalding at home have been developed, and that they could increase injury prevention activity and some parental safety behaviors.

The social media are a dynamic and interactive computer-mediated communication tool with a high impact in high-economy and middle-economy countries, and using social media in the health care context is gaining more and more popularity [20]. Social media websites, such as YouTube, Facebook, Twitter, etc., are popular sources of health information, especially for teens and young adults [21]. This made us take into consideration posting public messages on different social media in the future in order to raise awareness among adolescents and parents about potential risky behavior that can result in hand injuries with lifelong consequences.

CONCLUSION

Hand injuries in childhood are very common and can have devastating long-term consequences. As a result, it is of vital importance to develop better methods of prevention. These methods, which include not only raising awareness about this issue among parents and teenagers through social media and direct interaction with medical staff, but also the active involvement of teams of professionals, including social workers. These steps are of vital importance for the reduction of severe hand injuries in the pediatric population.

Conflict of interest: None declared.

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Повреде шаке код деце и адолесцената

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САЖЕТАК

Увод/Циљ Циљ овог рада је да одреди које су групе унутар дечје популације највише склоне повредама шака, као и да идентификује узроке повреда у циљу будуће превенције повреда које могу довести до инвалидитета.

Методе Спроведена је ретроспективна епидемиолошка студија на основу медицинске документације све деце лечене у нашој установи од 1. јануара 2010. до 31. децембра 2017; подаци су сакупљени и статистички анализирани коришћењем програма *SPSS*®. Значајност је дефинисана као *p* вредност < 0,05.

Резултати Укупан број пацијената је био 254, од тога 202 дечака и 52 девојчице, просечног узраста оба пола 10,13 година (распон година 1–17). Већина пацијената је била из урбаног подручја – 56,7%, а 43,3% њих је било из руралних области. У односу на месец у години када су се повреде дешавале идентификују се два пика – у јануару и мају. Десна шака је повређивана чешће (53,2%) у односу на леву, која је била повређена у 45,6% случајева, док су обе шаке биле повређене у 1,8% случајева. Изоловане повреде меких ткива (кожа, мишићи, тетиве) забележене су код 59% повређене деце, изолована коштана траума (преломи фаланги и метакарпалних костију) код 15,3%, док су мекоткивне и коштане повреде заједно чиниле 25,7%. Најчешће је повређиван мали прст, затим средњи прст и палац, а потом домали прст и кажипрст. Најтеже повреде, експлозивне ране, проузроковане су петардама и ватрометима, као и руковањем пољопривредним алатима и машинама.

Закључак Повреде шака у дечјем узрасту су честе и могу имати девастирајуће последице. Развој бољег превентивног програма подизањем свести о овом питању је од изузетног значаја.

Кључне речи: повреде шаке; деца; адолесценти; превенција

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Validation of the Montgomery–Åsberg Depression Rating Scale in depressed patients in Serbia

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SUMMARY

Introduction/Objective The aim of this study was the validation of the Montgomery–Åsberg Depression Rating Scale (MADRS) in patients in Serbia suffering from depression.

Methods Both test and retest situations have been conducted on 162 adult patients with major depressive disorder, and on 110 individuals that have not shown any type of mental disorder (control group). The sample included 58.8% male and 41.2% female participants, age between 20 and 79 years (M = 42.26, SD = 11.53) with no differences between groups in terms of participants' sex and age. The following instruments were used: MADRS, Hamilton Depression Rating Scale, and Brief Psychiatric Rating Scale.

Results MADRS has shown good psychometric characteristics: internal consistency, test-retest reliability, concurrent validity, and its discriminatory validity is adequate. Study also confirmed the one-dimensionality of the instrument. Statistically significant differences between the groups, in terms age and education, have been identified, but the effects of the differences were small.

Conclusion The MADRS scale has shown good psychometric characteristics in our study; thus, it may be used for the assessment of depressed states in Serbian patients.

Keywords: depression; Montgomery–Åsberg Depression Rating Scale; instrument validation

INTRODUCTION

According to the World Health Organization, in 2017, about 264 million people suffered from some form of depressive disorder, and depression is a leading cause of disability worldwide [1, 2]. Data from Serbia suggest that in 2014, 4.1% of the population had depressive disorder [3].

Apart from the clinical interview, measuring the degree of depression is mainly based on using the psychodiagnostic scales for assessing symptoms. Using these instruments is important because of objectivity in psychodiagnostics, quantitative expression of values (especially in clinical studies), and information relevant to the assessment of a clinical course and pharmacotherapy. However, there are several reasons why it is hard to evaluate depression. It might be because of the personality traits influence, physical disorders, comorbidities, and because depression symptoms can be a part of another diagnosis, like bipolar disorder or Parkinson disease [4, 5]. Finally, the results can also vary from one instrument to another, due to differences between self-assessment scales and clinician-administered scales, or some other methodological problem [6, 7, 8].

Depression assessment scales

Although various rating scales for depression are available (e.g., Hamilton Depression Rating Scale – HDRS, Montgomery–Åsberg Depression Rating Scale – MADRS, and Beck Depression Inventory – BDI), MADRS is one of the most frequently used scales for assessing severity of depression in research settings, clinical trials, and everyday primary care and clinical practice, and it has been translated into more than 24 languages [8, 9, 10]. The scale is applied and evaluated by psychiatrists in the form of a guided interview and it is suitable for monitoring change in the patient's state [9, 10]. Regardless if a structured interview is used or not, the scale has satisfactory reliability [11].

MADRS shows satisfactory psychometric characteristics, high agreement values between the examiners, and significant correlation with scores on HDRS, BDI, and the Mini-International Neuropsychiatric Interview [9, 10, 12]. A moderate to high association was shown between the patient's scores and the physician's scores [6, 7]; moreover, the patients perceived the scale as a useful tool that "added something" to the consultation with physicians [13]. Compared to HDRS, MADRS has shown greater sensitivity when distinguishing moderate and severe depression, and higher specificity than BDI-II in distinguishing individuals

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without depression in the primary care context [9, 14]. MADRS is also convenient when patients need to be tested efficiently and quickly, since the completion time is up to 10 minutes [9].

There are various opinions on factorial structure, because different studies have shown a different number of factors. A single-factor solution is the most frequent one [6, 15]. Other studies have shown that MADRS may have two or three factors, which represents different symptoms of depression, such as sadness and melancholy, or a general depression factor and motivational factor [16, 17]. The three-factor solution was proved useful in examining major depression disorder and in isolating subgroups of depressed patients with more pronounced symptoms [5]. There was even the four-factor model, in which the following factors were distinguished: covert sorrow, negative thoughts, alienation, as well as neurovegetative symptoms [18].

The main aim of this study was the validation of the MADRS psychometric properties in Serbian patients suffering from depression, and evaluation of its factorial structure, discriminative power, as well as external validity.

METHODS

Procedure

The study was conducted during a six-month period, between June and December of 2017, and the instruments were administered to the patients individually. The participation in the study was voluntary, anonymous, and informed consent was provided according to the provisions of the Declaration of Helsinki. The study protocol received ethical approval from the Ethical Committee, Dr. Laza Lazarević Clinic for Psychiatric Disorders in Belgrade, Serbia.

The first inclusion criterion for the clinical group was the diagnosis of unipolar depression without comorbidity (based on ICD-10 classification), diagnoses F32 and F33, except for the diagnosis with psychotic symptoms (F32.3 and F33.3). The other criteria were age of 18 years and above, a stable state in the previous two months, the treatment with antidepressants without modification of the therapeutic regimen in the previous two months, and Serbian as the native language.

The inclusion criteria for participants in control group were: absence of neurological and/or psychiatric disorders, age 18 years or above, Serbian as native language.

The clinical sample included patients from the Dr. Laza Lazarević Clinic for Psychiatric Disorders in Belgrade, Serbia. The diagnosis of mental disorder in this sample has been confirmed by the medical history records and anamnestic data. The absence of mental disorders in the control group has been established with the Brief Psychiatric Rating Scale (BPRS). Participants from both groups were included in the study only after they had read the information about the study and signed the consent to participate according to the Declaration of Helsinki. The control group sample was stratified and balanced based on sex and age data from the clinical sample. The sample was voluntary and consisted of the employees in public companies, such as the Belgrade Road Public Utility Company, Electric Power Distribution of Serbia, University Clinical Centre of Serbia. The remaining participants from this group were recruited via chain sampling.

Participants

The total number of participants was 272 – 162 from the clinical population (59.6%), and 110 in the control group (40.4%). There were 58.8% male and 41.2% female participants, their age being 20–79 years (M = 42.26, SD = 11.53). There were no differences between groups in terms of sex and age. Most of the participant had completed secondary school (59.1%), or had bachelor's degree (30% in the control, and 11.3% in the clinical group). The majority of participants with only elementary school was from the clinical group (10.6%), compared to the control group (2.7%); 16.4% of the non-clinical and 9.2% of the clinical sample had higher education.

Instruments

The study employed the following instruments.

MADRS [11] – contains 10 items in the seven-point Likert scoring format (from 0 – without difficulties, to 6 – significant difficulties). The level of depression is determined by the total sum, and it is classified as follows: 0–6 – without symptoms, 7–19 – mild depression, 20–34 – moderate depression, 34 and more – severe depression. MADRS has significant correlations with HDRS and BDI [9, 10, 12]. We used an original version of MADRS that was previously slightly modified after language and content validity test.

HDRS – serves to assess the degree of depression [19]. We used a 17-item version, determining depression according to the following scores: 0–7 – without depression, 8–15 – moderate depression, 16 and more – severe depression. The most recent validations of the instrument in Bangladesh and Poland showed satisfactory psychometric characteristics [16, 20]. Although it has long been considered a gold standard in the clinical assessment, over the years there have been several major problems with the scale [10]. The scale proved to be longitudinally unreliable and with a suboptimal number of responses offered. Also, the validity of the content is considered unsatisfactory due to somewhat outdated conception of depression. As a result, new versions have been made, with slightly different classification system of scores [21].

BPRS – a scale with 18 items, with a seven-point Likert scoring format (1–7). Studies have shown satisfactory reliability and validity, and it includes an assessment of the affects, thinking, anxiety, orientation, motor, and behavioral manifestations [22]. The main requirement for selecting subjects from the control group was a low score (< 30 points) on the BPRS as an indicator of the lack of psychopathology [22].

In addition to these instruments, we also used data obtained from medical history records. Other data (sex, age, and education) of participants from both groups were collected by an interview before the start of the test.

Statistical analyses and translation

We followed the recommendations for psychometric studies in which instruments are tested and validated [23]. For the translation of the scale into Serbian, a linguistic expert translated MADRS from English to Serbian, and this version was compared with the original in order to resolve potential discrepancies. Then, the instrument was translated back to English by another professional translator with a good command of both Serbian and English. The back-translation was compared with the original instrument and, after the necessary modifications, the scale was forwarded to further procedure.

The next step was that items' meaning and comprehensibility (*content validity*) were evaluated by two expert psychiatrists. All of the items were rated as appropriate and the final version of the scale was accepted.

Based on the recommendations for sample size [23, 24], we estimated that at least 100 respondents (minimum 10 subjects per item) were needed, since MADRS has 10 questions. When $\alpha = 0.05$, and the strength of the study $(1-\beta) = 0.80$, for testing the differences between two groups of t-tests (for example, subjects with or without depression), at least 51 subjects are needed per group, and testing the difference between three groups by the ANOVA test (e.g., respondents within the clinical group with mild, moderate, and severe depression) requires a total of 156 respondents. Based on all this and the calculations in the G*Power program (Heinrich-Heine-Universität Düsseldorf, Germany), the goal was to involve at least 160 subjects from the clinical population and at least 110 non-clinical respondents.

For the statistical analyses, we used exploratory factor analysis, t-test, Pearson correlation and intraclass correlation coefficient (ICC) for the reliability.

RESULTS

Factor structure

We used exploratory factor analysis with direct oblimin factor rotation. The analysis of the main components distinguishes one factor that explains 58.45% of the total variance (Table 1; Figure 1). All items have loadings above 0.50. Kaiser–Meyer–Olkin measure of representativeness was 0.90. Bartlett's sphericity test was statistically significant ($\chi^2(45) = 1698.03$, $p < 0.001$).

Analyzing individual items, item 6 (concentration difficulties) gives the largest share in the explanation of the variance with .072, item 2 with 0.71 (expressed sorrow), item 7 with 0.69 (difficulty in the commencement of activities), and item 1 with 0.69 (noticeable sorrow).

Table 1. Factor weights and explained variance in test and retest situation

Items	Test		Retest	
	Factor loadings	% of variance	Factor loadings	% of variance
MADRS1	0.830	0.689	0.836	0.698
MADRS2	0.844	0.712	0.822	0.676
MADRS3	0.692	0.479	0.584	0.341
MADRS4	0.695	0.483	0.722	0.521
MADRS5	0.652	0.425	0.647	0.418
MADRS6	0.846	0.716	0.804	0.646
MADRS7	0.832	0.693	0.852	0.726
MADRS8	0.772	0.596	0.787	0.619
MADRS9	0.727	0.528	0.732	0.536
MADRS10	0.723	0.523	0.717	0.514

MADRS – Montgomery–Åsberg Depression Rating Scale

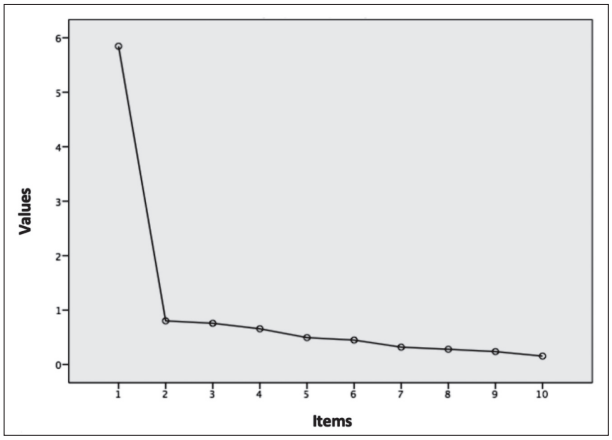

Figure 1. Diagram for the Montgomery–Åsberg Depression Rating Scale

Basic descriptive statistics are shown in Table 2.

Table 2. Descriptive data for Montgomery–Åsberg Depression Rating Scale (MADRS) in the clinical and the control group

MADRS	n	Mean	SD	Min.	Max.	skewness	kurtosis
Clinical group	162	13.28	11.8	0	51	1.01	0.2
Control group	110	1.7	1.96	0	8	1.31	0.46

Reliability analyses

The ICC is used in cases where there are more examiners or more repeated measurements in the research, and therefore it was suitable for this study. All of the measures that are given in Table 3 are referred to the combined measures of test and retest.

It is considered that each value of the ICC 0.75–0.90 is good, and values over 0.90 represent excellent test-retest reliability [25]. Cronbach's alpha values obtained at the first test ($\alpha = 0.84$) suggests high internal reliability of the scale considering the small number of items. The total test and retest scores also showed significant correlation ($r = 0.89$, $p < 0.01$). Therefore, all items, as well as the overall result, give good indication of reliability in repeated measurements, which suggests that longitudinal measurements can be considered reliable.

Table 3. Intraclass correlation coefficient (ICC) by items on the Montgomery–Åsberg Depression Rating Scale (all the items of the ICC are significant at the level of 0.01)

Items	M	SD	ICC	95% CI	
				Lower bound	Upper bound
1	2.06	2.93	0.87	0.83	0.9
2	2.01	2.83	0.84	0.8	0.88
3	2.18	2.48	0.88	0.85	0.91
4	1.75	2.78	0.9	0.87	0.92
5	0.78	2.01	0.86	0.82	0.89
6	1.45	2.52	0.87	0.84	0.9
7	1.55	2.54	0.86	0.82	0.89
8	1.41	2.65	0.88	0.84	0.9
9	1.39	2.19	0.84	0.80	0.88
10	0.56	1.72	0.87	0.83	0.9
Total	15.13	19.37	0.93	0.91	0.95

Discriminative sensitivity

The t-test results support the fact that there are statistically significant differences with large effect size between the clinical and non-clinical populations in both test and retest situation (Table 4).

Table 4. Differences between the clinical and the control group test and retest scores

Group	Clinical		Control		t	95% CI		Cohen's d
	M	SD	M	SD		Lower bound	Upper bound	
MADRS test	13.28	11.8	1.7	1.96	12.25*	9.72	13.45	1.37
MADRS retest	10.23	10.27	1.08	1.42	11.18*	7.53	10.76	1.25

MADRS – Montgomery–Åsberg Depression Rating Scale
* < 0.01

Discriminating power of the total score was shown to be satisfactory (canonical correlation 0.53; Wilk's lambda 0.52, $p < 0.001$; 77.2% of the participants correctly classified). The obtained results indicate that the area under the receiver operating characteristic curve is 0.878 (ranging 0.837–0.919). Cut-off score of 7 and above suggests the presence of depressive symptoms (mild depression category in original classification), since it showed the best sensitivity (0.636) and specificity (0.955).

External validation

In order to test external or concurrent validity of the scale, the scores on the MADRS were correlated with the scores on the HDRS scale. There was a statistically significant and very high positive correlation between these scores ($r = 0.96$, $p < 0.01$).

Demographic variables and MADRS scores

MADRS scores have shown no statistically significant differences between males and females (test: $t(272) = 1.80$, $p > 0.05$, retest: $t(272) = 1.78$, $p > 0.05$). A statistically significant difference in age groups was found ($F(3, 268) = 6.36$, $p < 0.01$), with medium effect size ($\eta^2 = 0.07$). The group of the oldest participants (above 52 years old) shows the highest scores ($M = 12.64$, $SD = 12.6$). Similar results are shown for the differences in education ($F(3, 248) = 9.68$, $p < 0.01$, $\eta^2 = 0.1$), where participants with the lowest education level (elementary school) show the highest scores ($M = 16.39$, $SD = 13.91$).

DISCUSSION

The research was conducted in order to validate the MADRS scale for Serbian patients, because it has wide application in assessing depressive disorders.

According to our findings, it can be concluded that MADRS has satisfactory internal reliability and psychometric characteristics in the test-retest situation. Other researchers have found that the MADRS scale has good psychometric characteristics, with the ICC varying from 0.89 to as much as 0.98, depending on the person who conducts an interview with the patient [12, 26]. The reliability of the entire instrument in our study was excellent (ICC = 0.93, r = 0.000), indicating that MADRS gives the same results on repeated measurements, and is good for monitoring, i.e., for use in longitudinal studies. The results show that all item intercorrelations in test and retest situations are also positive and strong (more than 0.60).

An analysis of the main components identified one factor explaining 58.45% of the variance, and it was confirmed that the MADRS measures a unique construct – depression. The one-dimensionality of the MADRS scale was previously confirmed in a large, multinational study involving depressed patients [6], as well as in other similar studies [12]. The items that proved to be most significant in factor analysis in both test situations in our study are difficulty with concentration, expressed sorrow, difficulty in starting the activity, and noticeable sadness.

MADRS shows significant differences between the clinical and the non-clinical population, which supports the discriminatory validity of the scale, in both test and retest situation. A recent study confirms, with rather high values of sensitivity and specificity, that the cut-off point for moderate depression is 20 (sensitivity 98%; specificity 96%), and the cut-off point for severe depression is 34 (sensitivity 98%; specificity 92%) [12]. In our study, a cut-off score of 7+ suggests the presence of depressive symptoms (mild depression category in the original classification).

What is particularly significant is the strong positive correlation between the MADRS and the HDRS-17, as it was also suggested by previous studies [8]. A number of studies comparing the MADRS and HDRS-17 have shown that the MADRS has a higher sensitivity to changes that occur under the effect of therapy [8, 27, 28].

It is important to note that there are certain differences in the scores in terms of demographic categories. No differences were found according to the sex criterion; however, the oldest participants and those with primary school education reported the highest scores. Medical conditions, cognitive deficits, loss of significant others,

and changes in social life associated with old age might decrease the applicability of some psychological treatments and influence the treatment outcome in elderly depressed people, but they can also influence the comprehension of the items, and an increased tendency towards depressive reactions upon testing [29]. The prevalence of depression is greater in individuals with lower socio-economic status and lower qualifications, which may be the reason why our results show that the participants with only primary school education report higher scores in comparison to other qualification levels [30].

A possible confounding variable of the present study is the effect of pharmacotherapy, as the change in the scores may depend on the type of the drug, the dosage of the drug, and the reactivity to the therapy. Other confounding variables relate to changes in the environment of respondents (improvement in relationships with fellowmen, the effects of psychotherapy, etc.).

CONCLUSION

The MADRS scale has shown good psychometric characteristics in our study; thus, it may be used for the assessment of depressive disorders in Serbian patients.

Conflict of interest: None declared.

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Валидација српске верзије скале Монтгомери–Осберг за процену депресије код депресивних болесника

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САЖЕТАК

Увод/Циљ Циљ ове студије била је валидација скале Монтгомери–Осберг за процену депресије код болесника у Србији који болују од депресије.

Методе И тест и ретест ситуације су спроведене на 162 одрасла болесника која имају дијагностикован депресивни поремећај, и на контролној групи од 110 особа које немају ниједан облик менталних поремећаја. Узорак је чинило 58,8% испитаника мушког и 41,2% женског пола, узраста између 20 и 79 година (M = 42,26, *SD* = 11,53), при чему није било разлике између испитиваних група по полу и годинама. Примењени су следећи инструменти: скала Монтгомери–Осберг за процену депресије, Хамилтонова скала за процену депресије, као и Кратка скала за психијатријску процену.

Резултати Психометријске карактеристике скале Монтгомери–Осберг за процену депресије, као што су интерна конзистенција, тест-ретест поузданост, екстерна валидност са Хамилтоновом скалом и дискриминаторна валидност, показале су се као адекватне. Студија је такође потврдила једнофакторску структуру инструмента. Добијене су статистички значајне разлике у скоровима између група по узрасту и образовању, али су ови ефекти разлика мали.

Закључак Скала Монтгомери–Осберг за процену депресије показала је добре психометријске карактеристике у нашој студији и као таква се може користити за процену депресивних стања код болесника у Србији.

Кључне речи: депресија; скала Монтгомери–Осберг; валидација инструмента

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Diagnostic performances and clinical usefulness of comprehensive non-commercial software for renogram analysis – values of renal output efficiency and normalized residual activity in suspected kidney outflow obstruction

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SUMMARY

Introduction/Objective Nuclear Medicine Section of IAEA has developed the software for dynamic renal scintigraphy, which allows calculation of advanced parameters of drainage: renal output efficiency (OE) and normalized residual activity (NORA).

The aim of this study was to validate IAEA software by comparing results of parameters of renal drainage in normal subjects against their established reference values and to assess diagnostic accuracy of OE and NORA in distinguishing between obstruction/unobstruction.

Methods Fifty-five patients with suspected obstruction and 36 kidney donors were investigated. Group A consisted of 24 obstructed kidneys, Group B of 37 kidneys with dilated urinary tract, and Group C of 72 normal kidneys. Forty-minute acquisition was applied. Furosemide was administered after 20 minutes. Post-micturition image was acquired at 50 minutes. The analyzed parameters were as follows: OE at 20 minutes (OE_{20}) and at the end of the furosemide test (OE_{40}), NORA at 20 minutes ($NORA_{20}$) and after micturition ($NORA_{PM}$). One-way ANOVA was used for evaluating the differences between the groups. Ability of OE_{40} and $NORA_{PM}$ to distinguish between obstruction/unobstruction was determined by ROC curve analysis. The sensitivity, specificity, area under the curve, and cut-off values were analyzed.

Results Excellent agreement of our results with established OE and NORA values was found. The difference between the groups was significant for OE_{20}, OE_{40}, $NORA_{20}$, and $NORA_{PM}$ ($p < 0.001$). Cut-off values for obstruction were 82% and 0.11 for OE_{40} and $NORA_{PM}$, respectively.

Conclusion IAEA software gives reliable analysis of diuretic renography and helps to better diagnose obstruction. IAEA should be encouraged to produce final version of the software and to release it online.

Keywords: radionuclide renography; uroobstruction; output efficiency; normalized residual activity

INTRODUCTION

Diuretic renography is an old nuclear medicine technique, which is still widely used in the diagnosis of upper urinary tract obstruction. The differentiation between obstruction and non obstructive dilatation is assessed by the analysis of the down-slope of renogram curve after injection of furosemide [1]. The advanced quantitative parameters of kidney drainage, i.e., renal output efficiency (OE) and normalized residual activity (NORA) were proposed some time ago. They were shown to be the least dependent of the underlying single kidney function in comparison with other parameters [2, 3].

Nonetheless, these parameters have not been routinely used, since the majority of software for the analysis of diuretic renography did not incorporate the tools for their calculation. In the meanwhile, the Nuclear Medicine and Diagnostic Imaging Section of the International Atomic Energy Agency (IAEA) has developed non-commercial software for renogram processing on a simple p-computer, which gave the opportunity of calculating OE and NORA [4]. However, neither was this software fully completed, nor was the quality of its quantitative indices validated in comparison with any commercial software package.

In this study we used MAG-3 and a specific time for injecting furosemide and studied the performances and clinical reliability of the use of IAEA Software Package in detecting urine flow obstruction. The aims were as follows: a) to validate the numerical outputs of this software by comparing the results of parameters of renal drainage in normal subjects against their established reference values, and b) to assess the diagnostic accuracy of OE and NORA in distinguishing between obstructed and patent upper urinary tract.

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METHODS

Patients enrolled in this study were referred from the Urology Department between November 2011 and July 2014 with the diagnosis of unilateral or bilateral urological disorder which caused the dilatation of the collecting system and suspected upper urinary tract obstruction. They had undergone ^{99m}Tc-MAG-3 dynamic scintigraphy with furosemide stimulation. The criteria for inclusion in the patients' groups were age over 18 years, renal function tests (serum creatinine level – sCr, creatinine clearance – cCr) and at least two imaging tests whose findings suggested obstruction. The exclusion criteria were recent renal or ureteral surgery and high grade of vesicoureteric reflux. There were 55 patients, 23 males and 32 females, aged 21–73 years (mean: 44.4 ± 16.0 years). For the control group, we selected 36 healthy subjects who were candidates for kidney donation. They had no structural abnormality of kidneys on ultrasound examination nor any history of kidney, urinary, or cardiovascular disorder, autoimmune disease, or diabetes. There were 16 males and 20 females (age range: 35–73 years; mean: 51.7 ± 10.6 years) in the control group.

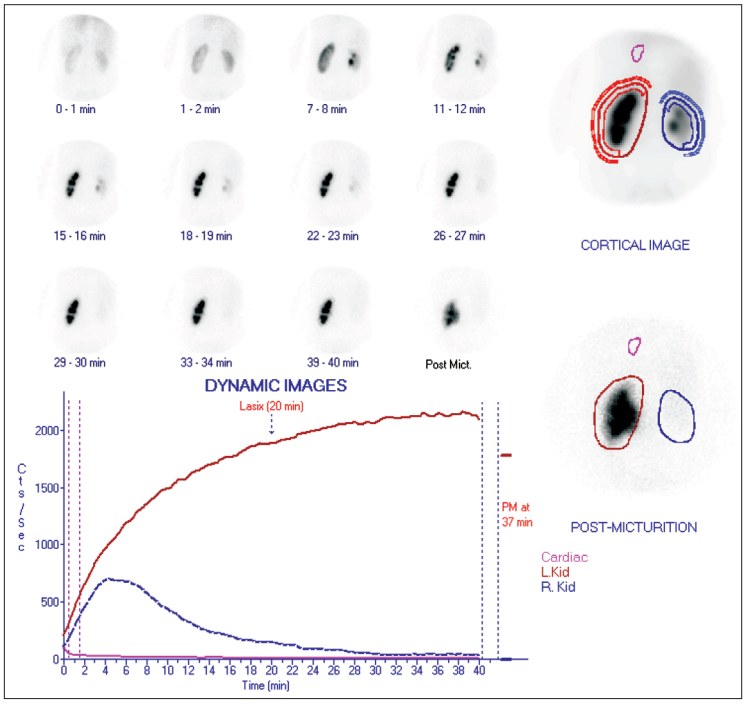

Figure 1. A structured display of IAEA Software Package review screen; serial 1-minute images of kidneys enable the estimation of tracer kinetics; composite parametric image with regions of interest over kidneys, left ventricle, and background; postmicturition image; renogram curves

Ethical approval for this study was obtained from the Ethics Committee of the University Clinical Center of Serbia (approval number: 668/6/2018), and the written informed consent from the patients was obtained.

Each subject received 500 ml of water 60 minutes before the study and emptied the bladder just before the acquisition. A large field of view γ camera (Siemens Orbiter 7500, Siemens, Erlangen, Germany) was set up with low-energy all-purpose collimator. The subject was in the supine position above the camera, which was positioned to include the left ventricle and both kidneys. A 40-minute acquisition protocol with 240 10-second images in 128 × 128 matrix size was applied. The dose of ^{99m}Tc-MAG-3 was adjusted for body weight, with a minimum of 74 MBq (2 mCi) and a maximum of 200 MBq (5.5 mCi), according to the respective guidelines [5, 6]. Furosemide was administered 20 minutes after the acquisition. Post-void static image of one minute duration was acquired 50 minutes after tracer injection.

Regions of interest were drawn over the left ventricle and both kidneys. The renal regions of interest included the kidney cortex and pelvis. From the generated renograms, the time to maximum activity (T_{max}) and to half maximum ($T_{1/2}$) were calculated. Differential renal function (DRF) was determined using the Rutland–Patlak plot method [7].

Three experienced physicians (two nuclear medicine specialists and one urologist) analyzed each patient and classified the kidneys into two categories. The division was based on the analysis of the pattern of excretion on diuretic renography after furosemide (by visual assessment of dynamic images and curves, T_{max} and $T_{1/2}$ values) and imaging tests other than renography (ultrasound, IVU, CT, MRU). Kidneys with poor drainage after furosemide and clinical/radiological signs of obstruction were classified into Group A. They were characterized by progressive accumulation of the radiopharmaceutical in the collecting system on dynamic scintigraphy and retention of the tracer on post-micturition images. Other imaging tests showed significant dilatation of pelvi-calyceal system and lack of appearance of radiology contrast media in the lower urinary tract. Group B consisted of hypotonic unobstructed kidneys with good drainage of the pelviureteric system after furosemide on dynamic scintigraphy images, followed by significant further drainage on post-micturition images. Radiology imaging tests revealed moderate pelvic dilatation and signs of patent urinary tract.

For the OE and NORA, the IAEA software package was used (Figure 1). These parameters were determined at two time points: OE at 20 minutes (OE_{20}) and at 40 minutes (20 minutes after furosemide injection, OE_{40}), NORA at 20 minutes ($NORA_{20}$) and on the post-micturition acquisition ($NORA_{PM}$).

Statistical analysis

For assessing the results of the research, descriptive and analytical statistics (IBM SPSS Statistics, Version 20.0; IBM Corp., Armonk, NY, USA) were used. The default level of significance was put below 0.05 level. We used the one-way ANOVA for evaluating the differences between the groups. The unpaired t-test was used to compare the values

Table 1. Parameters of ^{99m}Tc-MAG-3 renogram in normal kidneys

Values	T_{max} (min)	$T_{1/2}$ (min)	OE_{20} (%)	OE_{40} (%)	$NORA_{20}$	$NORA_{PM}$	DRF (%)
N	72	72	72	72	72	72	72
Mean	3.57	6.61	91.29	97.06	0.38	0.02	50.23
SD	0.66	1.75	2.77	1.25	0.11	0.01	3.43
Min	0.7	2.5	84	92	0.16	0.01	43
Max	5.2	11	97	98	0.69	0.06	57

DRF – differential renal function; T_{max} – time to maximum activity; $T_{1/2}$ time to half maximum activity; OE_{20} – output efficiency at 20 minutes; OE_{40} – output efficiency at the end of the furosemide test; $NORA_{20}$ – normalized residual activity at 20 minutes; $NORA_{PM}$ – normalized residual activity after micturition

between groups A and B. The relationship between OE_{20} and $NORA_{20}$ was assessed by Pearson correlation coefficient and linear regression analysis. The ability of the OE_{40} and $NORA_{PM}$ to distinguish between obstruction/unobstruction was determined by receiver operating characteristics (ROC) curve analysis. Sensitivity, specificity, the area under the curve (AUC) with 95% confidence interval, and cut-off values were analyzed.

Table 2. Output efficiency and normalized residual activity in kidneys with obstructed or dilated urinary tract.

Groups	OE_{20} (%)	OE_{40} (%)	$NORA_{20}$	$NORA_{PM}$
Group A (obstructed)				
n	24	24	24	24
Mean	49.61	66.18	2.4	0.32
SD	12.2	10.64	0.54	0.11
Min	31	47	1.73	0.17
Max	71	82	3.46	0.65
Group B (dilated)				
n	37	37	37	37
Mean	66.92	93.31	1.57	0.03
SD	12.75	3.70	0.66	0.01
Min	38	84	0.42	0.01
Max	91	98	3.51	0.06
p*	< 0.001	< 0.001	< 0.001	< 0.001

OE_{20} – output efficiency at 20 minutes; OE_{40} – output efficiency at the end of the furosemide test; $NORA_{20}$ – normalized residual activity at 20 minutes; $NORA_{PM}$ – normalized residual activity after micturition;
*significance level from comparison of kidneys with good and poor drainage

RESULTS

Subjects

Fifty-five patients presented with 61 hydronephrotic kidneys (49 patients with unilateral, six with bilateral HN). The underlying clinical diagnosis were pelviureteric junction narrowing (51%), renal calculus (38%), ureteral stenosis (4%), and other (7%). Twenty-four kidneys had the signs of obstruction and were classified into Group A, while Group B consisted of 37 kidneys with dilated but unobstructed upper urinary tracts. The control Group C consisted of 36 subjects with 72 renal units. In total, 91 subjects and 133 renal units were analyzed.

Parameters of renal washout in control subjects

There were 72 kidneys in Group C (36 on the left and 36 on the right side). In all kidneys, the DRF was normal, 43–57%. Table 1 shows the mean and standard deviation, the minimum and maximum values for T_{max}, $T_{1/2}$, OE_{20}, OE_{40}, $NORA_{20}$, $NORA_{PM}$, and DRF. As expected, the values for NORA were low, whereas OE was high.

Parameters of kidney washout in patients

Group A consisted of 23 kidneys, and Group B of 36 kidneys. The results of $NORA_{20}$, OE_{20}, OE_{40}, and $NORA_{PM}$ are shown in Table 2.

The one-way ANOVA comparison between the groups, taking normal Group C as the reference, showed significant difference for the OE_{20}, OE_{40}, $NORA_{20}$, and $NORA_{PM}$ ($p < 0.001$, Figure 2). Comparing the values between groups A and B, the significant difference was obtained for the values of OE_{40} and $NORA_{PM}$ ($p < 0.001$).

Table 3. Receiver operating characteristics analysis for output efficiency at the end of the furosemide test and normalized residual activity after micturition

Predictor variables	n	AUC	95% CI	p	Optimal cut-off value	Sensitivity (%)	Specificity (%)
OE40 (%)	61	0.992	0.934–1.000	< 0.001	≤ 82	98	91
NORAPM	61	1.00	0.852–1.000	< 0.001	> 0.10	97	95

OE_{40} – output efficiency at the end of the furosemide test; $NORA_{PM}$ – normalized residual activity after micturition; AUC – area under the receiver operating characteristics curve

Significant inverse linear correlation between $NORA_{20}$ and OE_{20} was obtained by linear regression analysis ($r = -0.982$; $y = 99.1 – 20.2x$) at 0.001 level. The dispersion of the values along the line of regression slightly increased when the quality of drainage decreased (Figure 3).

The ability of the OE_{40} and $NORA_{PM}$ to distinguish between obstructed and unobstructed kidneys were analyzed by the ROC curve analysis. The AUC with 95% confidence interval, optimal cut-off values, sensitivity, and specificity are summarized in Table 3.

DISCUSSION

In adult patients with suspected upper urinary tract obstruction, we studied the performances of the IAEA software for the comprehensive analysis of radionuclide renography and validated the reliability of its numerical outputs for characterizing kidney drainage, by comparing with reference values for ^{99m}Tc-MAG-3. The obtained results revealed excellent agreement with established normal ranges of OE and NORA. Normal kidneys presented with OE_{20} values higher than 83%, OE_{40} higher than 91%, $NORA_{20}$ lower than 0.70 and $NORA_{PM}$ lower than 0.07. In kidneys with obstruction, OE_{40} was lower than 83% and $NORA_{PM}$ was higher than 0.17. Furthermore, OE_{40} showed high sensibility and specificity in verifying insufficient drainage. The calculated cut-off values for predicting

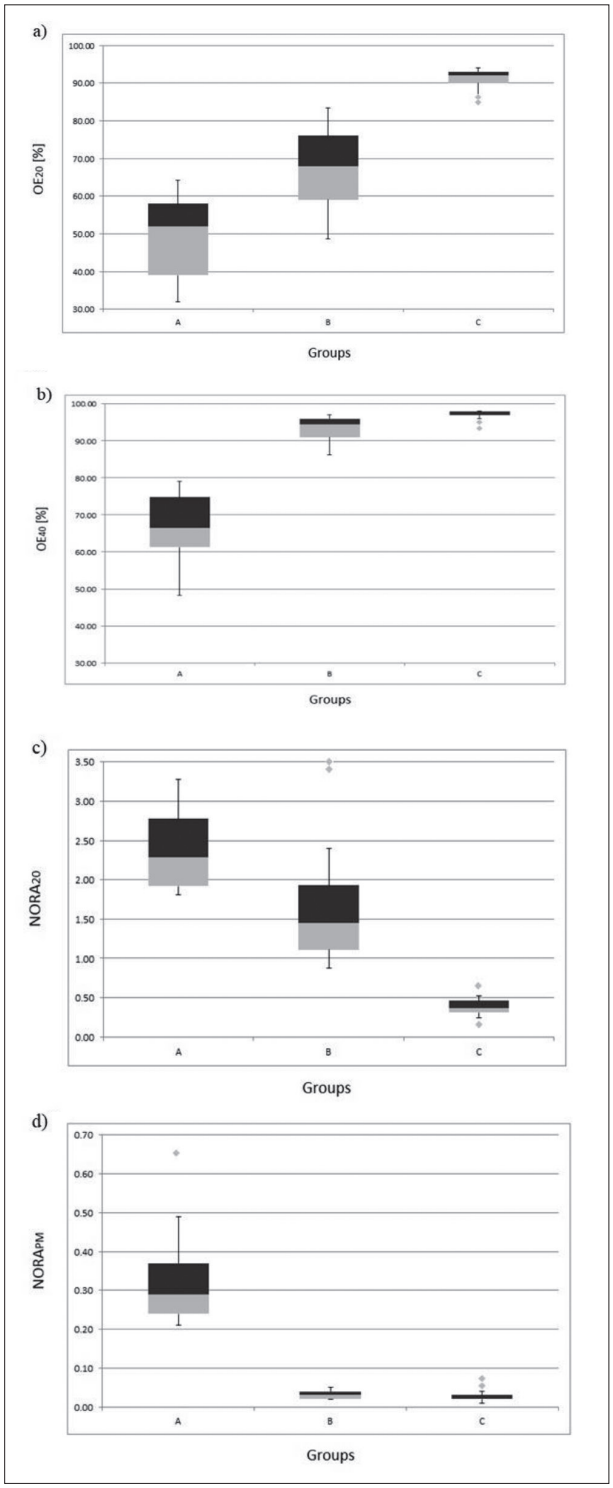

Figure 2. In a–d, the values of output efficiency OE_{20}, OE_{40}, normalized residual activity $NORA_{20}$ and $NORA_{PM}$ (postmicturition) are, respectively, represented for the groups of patients A, B, and C; OE is given in percentage and NORA in units

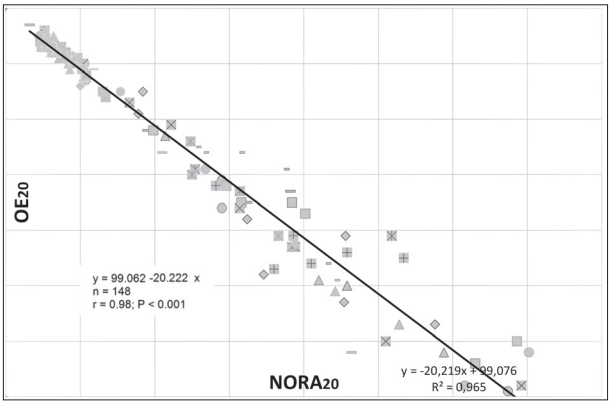

Figure 3. Correlation between output efficiency OE_{20} and normalized residual activity $NORA_{20}$; the Pearson's correlation coefficient was high ($r = -0.982$, $p < 0.001$)

poor drainage were shown to be ≤ 82% and > 0.10 for OE_{40} and $NORA_{PM}$, respectively.

The traditional way to analyze the diuretic renogram consisted of visual interpretation of dynamic images and time/activity curves, as well as the calculation of T_{max} and $T_{1/2}$ values [8]. The problem appears in cases of reduced renal function or grossly dilated renal pelvis when $T_{1/2}$ is prolonged, even in the absence of obstruction, which leads to equivocal findings of diuresis renography [9]. The output efficiency index and the normalized residual activity are two measurements that have been proposed by the International Scientific Committee of Radionuclides in Nephro-urology to compensate for slower rates of clearance due to reduced renal function [5]. Some commercial software packages incorporated the tools for calculating these two parameters, but users in developing countries could not afford them due to their high price. IAEA released the non-commercial Software Package for the Analysis of Scintigraphic Renal Dynamic Studies as a draft version in 2010 [4]. However, to date, the software has not been completed, probably due to the lack of interest in nuclear medicine centers in developed countries to apply the software, since their departments are equipped with high-quality commercial software packages. In our department, there has been considerable interest to apply the advanced analysis of diuretic renography. To the best of our knowledge, this is the first study on the validation of numerical indices of the IAEA software in patients with impaired drainage.

In the previously published studies about OE and NORA, various protocols were used, with the differences in duration of acquisition and in the time of diuretic challenge. This invalidates the comparison between studies and avoids the determination of the cut-off values of these parameters for differentiation between obstruction/unobstruction. In the newest guidelines for diuresis renography, three time points were specified for the calculation of renogram parameters: 20 minutes after the start of the acquisition, 20 minutes after the diuretic challenge, and on the post-micturition scan. The current version of the IAEA offers the calculation of OE_{20} and OE_{40}, $NORA_{20}$, and $NORA_{PM}$ [5, 10]. According to these time points, we calculated the present results.

The normal ranges for parameters of ^{99m}Tc-MAG-3 renogram were reported in several studies, mainly for T_{max} and $T_{1/2}$ [11–15]. The results calculated in our study with the use of IAEA software showed substantial agreement with these values (Table 4).

Table 4. Comparison with related studies for T_{max} and $T_{1/2}$

Study (year)	Tmax (minutes)			T1/2 (minutes)		
	n	Mean	SD	n	Mean	SD
[11] (1994)	36	3.6	2.2	36	6	2.5
[12] (2002)	82	3.2	0.6	-	-	-
Jung and coworkers (2005) [13]	22	3.8	1.2	22	6.2	2.5
[14] (2006)	106	3.8	1.9	106	6.5	4.1
[15] (2015)	48	3.1	0.5	-	-	-
Present study	72	3.6	0.7	72	6.6	1.7

T_{max} – time to maximum activity; $T_{1/2}$ time to half maximum activity

For the OE, in the study that validated this index as an objective quantitative parameter of kidney drainage, Chaiwatanarat et al. [2] reported the normal values in 22 kidneys of healthy control subjects to be 91.6 ± 4.6%, which is in complete agreement with our results. In obstructed kidneys, they obtained somewhat lower values in comparison with the present study, probably due to shorter time for diuretic challenge (30 minutes acquisition instead of 40 minutes in our protocol). In the study of output efficiency as a method for clarifying equivocal renograms, the 30-minute acquisition protocol was also applied and the reported cut-off value for excluding obstruction was lower than that in our study [16].

The NORA index was proposed as a robust parameter of renal drainage and simpler for calculation than OE. This parameter has not been widely assessed in the literature. More frequently used was the residual activity index expressed as a percentage of the maximal activity, but it does not take into account the value of renal clearance [17]. The reported normal threshold for $NORA_{20}$ was 0.70, which is identical with the result of the present study [18].

We correlated the values of NORA and OE at calculated at 20 minutes and obtained high values of Pearson correlation coefficient, since a significant correspondence was reported between these two parameters in the literature [19]. This correlation confirmed the statement of the possibility to replace the OE with NORA, when deconvolution method for calculation of OE could not be applied or is not available [20].

We have determined the optimal cut-off values for OE_{40} and $NORA_{PM}$ to distinguish between hypotonic unobstructed kidneys and kidneys with obstruction. They were similar with the previously reported cut-off values for obstruction and yielded a sensitivity and specificity of almost 100%, thus affirming the use of these parameters in evaluation of kidney drainage [18].

CONCLUSION

This study demonstrates that the implementation of the new algorithm for quantification of renal drainage, incorporated in the IAEA software package, provides comprehensive, high-quality quantitative analysis of diuretic renography. Renal output efficiency and normalized residual activity are accurate parameters of renal drainage, which contribute to the diagnosis of kidney outflow obstruction. The calculation of these quantitative indices should become a part of routine analysis of dynamic renal scintigraphy. They would facilitate the comparison between studies during follow-up and monitoring the response to surgical treatment. In addition, the use of this software can help to standardize the protocols for acquisition and processing of the diuretic renography and to avoid the measurement of excretory parameters at various times after diuretic challenge, which hampers the comparison of studies between centers. The harmonization of the scintigraphy reports could enable the exchange of quantitative data between physicians and departments. We would appeal to the Nuclear Medicine and Diagnostic Imaging section of the IAEA to complete the work on the software and to release it through the IAEA website.

Conflict of interest: None declared.

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Клиничка евалуација новог софтвера за анализу динамске сцинтиграфије бубрега – значај ефикасности бубрежне елиминације и нормализоване резидуалне активности у дијагностици опструкције уринарног тракта

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САЖЕТАК

Увод/Циљ У Одсеку за нуклеарну медицину Међународне агенције за атомску енергију (МААЕ) направљен је софтвер за анализу динамске сцинтиграфије бубрега, који омогућава израчунавање нових, прецизнијих показатеља бубрежног излучивања – ефикасности елиминације (ЕЕ) и нормализоване резидуалне активности (НОРА).

Циљ нашег рада је валидирање софтвера МААЕ поређењем вредности параметара реонограма код здравих испитаника са њиховим референтним вредностима и процена значаја ЕЕ и НОРА у диференцијалној дијагностици уроопструкције.

Методе Анализиран је 91 испитаник – 55 болесника са суспектном опструкцијом уринарног тракта и 36 давалаца бубрега. У Групи *A* су била 24 опструктивна бубрега, у Групи *B* 37 бубрега са неопструктивном дилатацијом, у Контролној групи *C* 72 нормална бубрега. Сцинтиграфија је рађена током 40. минута после *i.v.* убризгавања ^{99m}*Tc-MAG*-3, фуросемид је убризган у 20. минуту, а постмикциона сцинтиграфија снимљена у 50. минуту. За обраду је коришћен софтвер МААЕ. Анализирани су ЕЕ у 20. минуту (EE_{20}) и 20 минута после фуросемида (EE_{40}), НОРА у 20. минуту ($НОРА_{20}$) и после микције ($НОРА_{ПМ}$). У процени резултата истраживања коришћене су методе дескриптивне и аналитичке статистике.

Резултати Поређење наших резултата са референтним вредностима ЕЕ и НОРА показало је висок степен сагласности. Разлика између група је била статистички значајна за EE_{20}, EE_{40}, $НОРА_{20}$ и $НОРА_{ПМ}$ ($p < 0,001$). *Cut-off* вредности за дијагнозу опструкције су биле 82% за EE_{40} и 0,11 за $НОРА_{ПМ}$.

Закључак Примена софтвера МААЕ повећава дијагностичку тачност диурезне реонографије и доприноси прецизнијој дијагностици уроопструкције. С обзиром на то да одељења нуклеарне медицине у многим земљама не поседују савремене софтвере за сцинтиграфију бубрега, било би значајно да МААЕ омогући преузимање софтвера преко електронског сајта.

Кључне речи: радиоизотопна реонографија; уроопструкција; ефикасност елиминације; нормализована резидуална активност

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Olecranon aperture of the humerus – a morphometrical study

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SUMMARY
Introduction/Objective Olecranon aperture is a variable opening in the septum between the olecranon and coronoid fossae. Its frequency varies largely in different populations and knowledge of its presence may have clinical implications.
The objective of our study was to determine its prevalence in a sample of Serbian population and to investigate its morphology and morphometrical features, as well as its relation to the distal end of humerus.
Methods A material used were 70 dry human humeri from the bone collection of the Department of Anatomy, Faculty of Medicine, University of Niš. We analyzed the presence, shape, transverse and vertical diameter of the aperture, its distance to the tips of the epicondyles from medial border (MB) and lateral border (LB), as well as the distance between epicondyles (EW) and translucency of the septum in the bones with no aperture. Vernier caliper was used for measurements of the diameters and distances.
Results Eight olecranon aperatures were observed in seven bones (10%), seven on the left and one on the right side. Half of them were oval-shaped, while round, triangular, and irregular shape were found. Translucent septum in humeri with no aperture was present in 67.1% of the sample. There were no significant differences between MB and LB, neither between EW in bones with aperture and with septum.
Conclusion Our study presented the rare data about the frequency of olecranon aperture in Serbian population, suggesting that robusticity of the humerus is not related to the presence of the olecranon aperture.
Keywords: human anatomy; anthropology; supratrochlear foramen; septal aperture; fracture

INTRODUCTION

The coronoid fossa and the olecranon fossa of the distal epiphysis of humerus are separated by a thin bony septum which may occasionally be perforated, thus forming the variable opening [1, 2]. This inconstant perforation is commonly known as "septal aperture", "olecranon aperture," "olecranon foramen," "supratrochlear aperture" or "supratrochlear foramen," the last one being a term proposed to be incorporated into the Terminologia Anatomica, but it has not been added to its Second Edition which is pending approval [1–11]. Recent studies suggested that this opening should be considered an aperture, not a foramen [2, 8]. A foramen is rather a conduit for the passage of neurovascular elements, while an aperture represents an opening in the bone [8]. Therefore, it was recently suggested that this anatomical variant is labelled as "olecranon aperture," considering the fact that it is not giving passage to any anatomical structure [2]. We also found this term more precise, due to relation of the aperture to the olecranon, as well as being more distinctive than "supratrochlear" one, which may be mistaken for the elements located on the frontal bone.

The incidence of the olecranon aperture of the humerus (OAH) among humans is highly variable and ranges 0.3–58% in different populations [8]. The literature data shows substantial discrepancies between various human subpopulations and ethnicities, which varies from around 11% in European populations, the lowest regional prevalence according to the large meta-analysis [2, 12], to 58% in Native Americans from Arkansas, USA [8].

The thin lamina is present until the age of seven, after which the bony septum may be absorbed and substituted by dense regular connective tissue [8]. The aperture is showed to be more frequent in women, on the left side [13]. There are many hypotheses on the origin of the OAH, based on mechanical features, robusticity, metabolic factors, genetics, and atavistic traits; yet none has offered an explanation plausible or convincing enough.

The olecranon aperture is a nonmetric skeletal trait important in anthropology, which may be important for investigating familiar inheritance, whereas its analysis in medicine may find application in radiology and orthopedic surgery [5]. To the best of our knowledge, the only data reported within the area of the Republic of Serbia is one archeological case, a

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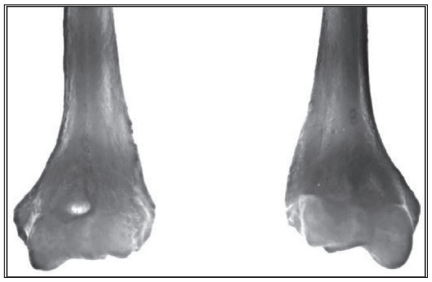

Figure 1. Translucent (left) and opaque (right) septum between the olecranon and coronoid fossae

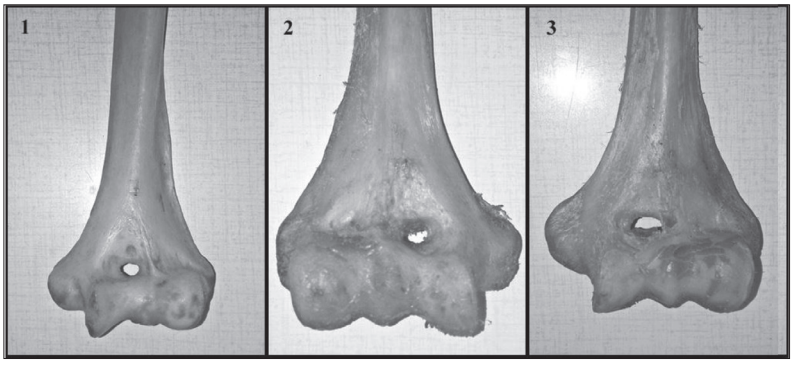

Figure 2. Distal ends of humeri with various shapes of the olecranon aperture (1 – oval; 2 – triangular; 3 – irregular)

skeleton 4th–6th century (date estimated), excavated in Kikinda, with a bilateral aperture found [10]. Therefore, this study is aimed to determine the incidence of the OAH in a sample of Serbian population, as well as morphometric characteristics of the aperture in relation to its size, shape, and distance to the epicondyles, and to assess the relation between the epicondylar width (EW), as a measure of bone size, and presence of the OAH.

METHODS

The study included 70 bilateral dry humeri of unknown age and sex from the osteological collection of the Department of Anatomy, Faculty of Medicine, University of Niš, Serbia. The research was done in accordance with the standards of the local committee on ethics. The bones chosen for sample group were with no pathological changes and ante- or post mortem fractures. Bone healing features, such as a callus, indicated premortem trauma, while sharp borders or surfaces were used to identify postmortem damage. With the help of transmitted light from posterior to anterior, we analyzed the opacity and translucency of the bony septum in the bones with no OAH detected (Figure 1), and determined presence and shape of the OAH, where applicable (Figure 2). Vernier caliper with a scale division of 0.02 mm was used to measure the transverse diameter (TD) and vertical diameter (VD), the distance of the medial epicondyle to the MB of the OAH, distance of the lateral epicondyle to the LB of the OAH, and the EW. The two observers took measurement three times independent of each other and the mean measurement was used. The EW was statistically compared between bones with and without the OAH. Student's t-test and descriptive statistics (mean, standard deviation, minimum and maximum values) were obtained using the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA)

RESULTS

In the sample of 70 bones the olecranon aperture was detected in seven humeri (10%). There were two apertures observed in one bone, which makes total of eight measured OAH. Seven apertures were present on the left side, and only one case on the right side. The most common shape of the OAH was oval (four). We also noticed two round apertures, one triangular and one irregularly shaped OAH. The translucent septum was found in 47 humeri (67.1%), 28 on the left side, and 19 on the right side. The opaque septum was detected in 16 bones (22.9%), eight on each side (Table 1).

Table 1. Frequency of olecranon aperture of the humerus (OAH) and translucent and opaque septum

n = 70 humeri	Left side	Right side	Total
Bones with OAH	6 (8.6%)	1 (1.4%)	7 (10%)
Translucent septum	28 (40%)	19 (27.1%)	47 (67.1%)
Opaque septum	8 (11.4%)	8 (11.4%)	16 (22.9%)

The mean TD of the OAH was 5.25 ± 3.62 mm and the mean VD was 3.33 ± 1.93 mm. Average distance of the medial epicondyle to the MB of the OAH was 26.92 ± 5.03 mm, while average distance from the lateral epicondyle to the LB of the aperture was 29.59 ± 4.22 mm, but not significantly larger (p = 0.13; threshold of significance 0.05) (Table 2).

Mean EW in the bones with OAH present was 58.97 ± 5.53 mm, which was not statistically different (p = 0.08; threshold of significance 0.05) from average EW in the bones with no aperture (61.03 ± 3.20 mm) (Table 2).

Table 2. Measurements of olecranon aperture and distal end of humerus (in mm)

Values	TD	VD	MB	LB	EW with OAH	EW with septum
Mean	5.25	3.33	26.92[a]	29.59	58.97[b]	61.03
SD	3.62	1.93	5.03	4.22	5.53	3.20
Min–max	1.32–11.96	1.22–7.68	19.92–35.48	24.14–35.50	50.50–65.74	56.14–67.86

TD – transverse diameter; VD – vertical diameter; MB – distance from the medial border of the aperture to the tip of the medial epicondyle of the humerus; LB – distance from the lateral border of the aperture to the tip of the lateral epicondyle of the humerus; EW – epicondylar width; OAH – olecranon aperture of the humerus;
[a]p = 0.13 *vs.* LB (no statistical significance)
[b]p = 0.08 *vs.* EW with septum (no statistical significance)

DISCUSSION

The debate in literature about the name of this opening between the olecranon and coronoid fossae of the humerus is whether it is an aperture or a foramen. It is reported that *in vivo* it is occupied by connective tissue which is not perforated by any nerve or blood vessel. Most studies were performed on cadaveric and archeological human remains, which are subjected to maceration and decomposition of softer tissues respectively, which misled earlier investigators to consider it constantly open and consequently name it as a foramen [8].

Meta-analysis showed that the overall pooled prevalence of the OAH was 21.9%, with studies conducted in African populations reporting the highest prevalence (31%). Data reported on the samples located in or descending from Europe had the lowest prevalence (11.1%) [2]. Table 3 shows frequencies in different populations all over the world, where the samples of Greek population strangely present minimum and maximum prevalence (0.3–21.6%) [1, 3, 4, 6, 9, 13–19]. The results of our study (10%) are within a range expected for European populations, although more extensive sample would offer more information if the prevalence leans to lower numbers, such as medieval Slavic Polish population and neighboring Romanian one, or higher frequencies, such as Greek and Turkish groups, particularly along with analyzing population affinity and migrations, which were largely present in the history of the area our sample belongs to [5].

We found the OAH to be dominant on the left humeri, which is in concordance with statistically significant difference shown in 41 studies [2]. There are reports with the right side being more frequent or bilateral compared to the left side [12, 19]. The majority of the OAH found were oval, then round, and one triangular and irregular each. These findings and proportions strengthen earlier reports [2, 15, 19, 20], although some unusual shapes were also reported, such as sieve-like, rectangular or reniform [6, 18]. The female samples are usually shown as being more predilected for the OAH presence, and even slightly higher frequency in males is a rare finding [1, 2, 4, 5, 6, 13].

The bones with no septum perforated were investigated for its translucency. Our results (67.1% translucent *vs*. 22.9% opaque) are among the ranges presented in the literature [7]. High frequency of the translucent septa in the present study may suggest higher probability of developing olecranon aperture present in the population, which should be investigated in a larger and more representative sample.

The size of the aperture seems to differ in various populations. Results by Turkish researchers [7, 9] presented the largest TD (average 6.09 ± 2.43 mm and 6.7 ± 2.20 mm in the right male humeri, as well as in the Nigerian population [18] (6.82 ± 2.92 mm in left side bones), while the smallest ones were found in Chinese [15] (mean 3.26 ± 1.15 mm in right humeri) and Brazilian [1] cases (average 2.33 ± 1.23 mm in left side samples). Smaller apertures in latter study are believed to be due to the heterogeneity of Brazilian population as a consequence of mixing native people with the colonizing and immigrating nations [1]. In our study, the mean TD was 5.25 ± 3.62 mm, which is similar to another Turkish study (5.23 ± 3.74 mm in the right humeri, 4.80 ± 2.65 mm in the left humeri) [20], and in a range with the pooled results on 1086 bones (5.06 ± 1.08 mm, 5.45 ± 1.31 mm, for the right and left sides respectively), with no significant difference shown between the right and left sides [2]. The only literature data from our country are from excavated remains dated 4th–6th century where the TD was 18 mm on the right side, and 11 mm on the left side [10], which partially corresponds to our maximum value found in the left humerus (11.96 mm), as well as to the only finding within the recent bone material (10.4 mm), presented in the tabular literature data comparison [7]. This ancient material measurement may be also compared to the study on the medieval skeleton materials in England, where the values were up to 21 mm [3].

Table 3. Frequencies of the olecranon aperture of the humerus in different populations

Study authors	Populations	Prevalence (%)
Papaloucas et al. [9]	Greek	0.3
Varlam et al. [14]	Romanian	1.8
Hirsh [15]	White American	4.2
Glanville [15]	European	6
Glanville [9]	Dutch	6.1
Benfer and McKern [9]	American	6.9
Mays [3]	English	6.9
Hrdlicka [15]	Irish	7.4
Myszka et al. [4]	Polish	7.5
Oztürk et al. [9]	Egyptian	7.9
Koyun et al. [9]	Turkish	8.6
Akabori [15]	Ainus	8.8
Hrdlicka [15]	German	8.8
Hrdlicka [9]	Italian	9.4
Li et al. [15]	Chinese	10.3
Erdogmus et al. [9]	Turkish	10.8
Akabori [9]	Korean	11
Ndou et al. [16]	European	16
Bradshaw et al. [13]	Portuguese	16.8
Ming-Tzu [9]	Chinese	17.5
Akabori [9]	Japanese	18.1
Krishnamurthy et al. [15]	Eskimo	18.4
Bradshaw et al. [13]	Greek	21.6
Sablan et al. [17]	Arab	21.6
Hirsh [15]	African American	21.7
Chagas et al. [1]	Brazilian	22.5
Mathew et al. [6]	Southern Indian	24.5
Sablan et al. [17]	Yazidi	26
Sunday et al. [18]	Nigerian	27.7
Sablan et al. [17]	Kurdish	30.6
Ndou et al. [16]	Xhosa	33
Nayak et al. [19]	Indian	34.4
Ndou et al. [16]	Zulu	37
Krishnamurthy et al. [15]	Mexican	38.7
Ndou et al. [16]	Tswana	39
Ndou et al. [16]	Sotho	41
Hrdlicka [15]	Australian	46.5
Glanville [9]	Tellem	47
Hirsh [9]	Native American	58

Mean VD in our research was 3.33 ± 1.93 mm, which is smaller than pooled results (4.09 ± 0.86 mm on the right, 4.43 ± 0.83 mm on the left side) and majority of the reported data (4.86 ± 1.32 mm; 4.21 ± 1.29 mm; 3.81 ± 0.97 mm) [7, 19, 20], only to be compared to the right male humeri (3.27 ± 1.46 mm) in Portuguese population [13], left side bones in Indian sample (3.37 ± 1.25 mm) [6] and right apertures in the Nigerian group (3.33 ± 1.04 mm) [18].

The distance between the borders of the aperture and the tips of the epicondyles is suggested in the literature to determine the position of the OAH. Our results (MB 26.92 ± 5.03 mm, LB 29.59 ± 4.22 mm) indicate that the apertures in our study were more medially located, but the difference was not statistically significant (p = 0.13). Other researchers have also observed the OAH to be positioned nearer to the medial epicondyle [7, 9, 16, 19]. The South African study on several ethnic groups reported that the population group with the largest TD had significantly smaller MB and LB compared to the other investigated groups, which was speculated to be due to the smallest epicondylar breadth, as a feature of size and robustness, supporting the findings that the OAH is more prevalent on the left and among females [16]. Therefore, we included the EW in our morphometrical analysis and compared the bones with or without septum, to check if there is any significant relation between the width of the distal epiphysis and the presence of the aperture, as already reported [5]. Mean EW in the bones with the OAH in present study was 58.97 ± 5.53 mm, which was not significantly smaller than in bones with the septum (61.03 ± 3.20 mm), so our data, supported by other researchers too [3, 13], could not provide evidence that olecranon aperture is more frequent in gracile bones, thus not being in accordance with the robusticity hypothesis of the origin of the olecranon aperture.

Prior knowledge of anatomical variants may have an importance in clinical practice, as it may be an unpleasant finding during a diagnostic or therapeutic procedure [21]. Radiologists and orthopedists could misinterpret the aperture as a lytic or cystic lesion, due to a relative radiolucency [1]. Assessment of the range of motion in the joint is a common method in physiotherapy to estimate a grade of an impairment [22]. Previous studies reported that individuals with the OAH might present overextension in lax and very mobile elbow joint [1]. This hyperextension may be accounted on increased elasticity of the collagen fibers or weaker triceps, but not on the size of the proximal ulna, as well as not on the strength of brachialis, which may indicate a supposed dominant role of the olecranon process in the OAH formation [13, 23].

There was suggested that the presence of this aperture is associated with a narrow and short medullary canal of the humerus thus may having the influence in the choice of adequate surgical procedure, although a recent study found no relation between the OAH presence and the width of the medullary canal [24, 25]. Sahajpal and Pichora [26] suggested that an olecranon aperture might act as a stress riser in healthy humerus thus leading to an atypical fracture-in low energy injuries. Furthermore, increased stress may modify the fracture pattern of the distal humerus. Therefore, knowledge on the frequency and causes of the OAH may alter surgical plan in patients with this anatomic finding [13, 26].

Supracondylar fractures are among the most common elbow fracture in pediatric patients where the intramedullary fixation is commonly indicated as a surgical treatment [27]. Nevertheless, the entry point for intramedullary pin insertion is controversy in patients with the presence of the OAH in order to avoid the bone damage and the pin incarceration [1]. Antegrade insertion of intramedullary pins is suggested to have lower intraoperative and postoperative fracture potential [28] thus to be safer approach in relation to retrograde medullary nailing [9, 29].

The knowledge about OAH could have an importance in later studies about defining the safe zones for screw insertion in distal humeral fractures internal fixation [30]. There could be defined the minimal suggested distance between the screw and the border of the OAH during the intraoperative X-ray checks thus avoiding the threads to pass out of the cortical bone.

The anatomical finding of OAH could also have an impact in later elbow joint endoprosthesis constructions, suggesting that the hole of the prosthesis component may not have to be avoided in a position analog to the OAH anatomic position.

CONCLUSION

The results of our study presented the frequency and morphometrical features of the variable OAH. The prevalence of 10% is comparable to other populations and indicates that the knowledge of this variable opening should not be neglected in preoperative planning and choosing an adequate surgical approach, as well as in interpretation of radiological findings. Our morphometric analysis found no relation between the presence of the olecranon aperture and robusticity of the humerus. In addition, our data contribute to the recent morphological, biomechanical, forensic, and anthropological studies, although etiological factors regarding this anatomical variant still remain uncertain.

ACKNOWLEGMENTS

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Conflict of interest: None declared.

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Отвор лактичног наставка на раменици – морфометријска студија

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САЖЕТАК

Увод/Циљ Отвор лактичног наставка је варијабилни отвор на прегради која раздваја јаму лактичног наставка и венчасту јаму раменице. Његово присуство веома варира у различитим популацијама и познавање његовог присуства може бити од клиничког значаја. Као циљ је постављено одређивање преваленце овог отвора на узорку српске популације, испитивање његове морфологије и морфометријских параметара, као и његовог односа према структурама доњег окрајка раменице.

Методе Као материјал је коришћено 70 људских раменица из остеолошке колекције Катедре за анатомију Медицинског факултета Универзитета у Нишу. Анализирали смо присуство и облик отвора, његов попречни и вертикални пречник, растојање унутрашње и спољашње ивице отвора у односу на одговарајући чвор раменице, као и растојање између чворова раменице и провидност преграде на костима без отвора. За мерење је коришћен нонијус.

Резултати Осам отвора је било присутно на седам костију (10%), од тога седам на левој и једна на десној страни. Половина отвора је била овалног облика, док су остали били округлог, троугластог и неправилног облика. Провидна преграда на костима без отвора је забележена на 67,1% узорка. Није забележена значајна разлика између растојања унутрашње и спољашње ивице отвора од одговарајућег чвора раменице, као ни између растојања између чворова раменице на костима са отвором и без њега.

Закључак Наше истраживање пружа ретке податке о заступљености и морфометријским карактеристикама отвора лактичног наставка у српској популацији, указујући на то да робусност раменице није повезана са присуством овог отвора.

Кључне речи: анатомија човека; антропологија; супратрохлеарни отвор; септални отвор; фрактура

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

A standstill of the continuing medical education in Serbia 2011–2017

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SUMMARY
Introduction/Objective Continuing Medical Education (CME) is a crucial element to keep the level of professionalism in the three key fields of medical education: pre-clinical, clinical, and public health. The profile of CME in Serbia has been analyzed for the 2011–2017 period.
Methods Between 2011 and 2017, 11,557 courses of CME have been submitted for accreditation, described by 26 variables. Due to the predominance of nominal data, we employed a principal component analysis (PCA) using the nonlinear iterative partial least squares algorithm (PCA/PLS) to arrange the 16 variables with complete information in such a way that most influential factors could be displayed and ranked. The analysis was done with TIBCO Statistical Software.
Results The Faculty of Medicine of Belgrade takes the top position among the medical faculties in Serbia with 569 courses or 47.9% (n = 1187; 2011–2017), whereas non-educational institutions with 86.2% of all courses (n = 11,514) are the most dominant providers. Clinical topics dominate the thematic spectrum with 59.7%. Between 2012 and 2017, the total number of courses offered diminished by 16.9%. A PCA of 16 potential determinants of CME reveals that the most relevant ones are duration, credit points, price, and number of lecturers.
Conclusion For the last decade, a standstill or even a regression in the development can be observed. Especially the faculties of medicine in Serbia, as well as other major providers, should reconsider the entire structure of their administrative organization and initiate innovative development.
Keywords: continuing medical education; accreditation; evaluation; faculties of medicine; Serbia

INTRODUCTION

Over the last 50 years, Continuing Medical Education (CME) attracts the attention of both professionals and scientists as a tool, which is applied either mandatory or voluntary to maintain and upgrade physicians' competences and hence the quality of health care [1]. In 2015, Cervero and Gaines [2] provided and updated synthesis of systematic reviews to present the significance of CME and its positive impact on physicians' performance and clinical outcomes. Today, CME is one of the essential mechanisms in setting targets for high-quality health care and equipping the health care staff to perform corresponding to quality standards [3]. Accountability and financing arrangements play a role in strengthening CME. Particularly in low- and middle-income countries, CME is a valuable option introduced by governments and professional organizations to improve the quality of health care [4]. Besides the effects of CME at these macro- and meso-levels, it has potential at the micro level to improve health workers' motivation and staff retention by serving as an incentive.

CME is a composite part of health workforce development, and though the needs for a comprehensive system of CME in each country have existed for many years, this topic only recently became the object of scientific analysis. Several studies pointed to the diversity among countries in the system of CME organization [5, 6, 7]. The lessons of good practice are based on the existence of national or regional accreditation of training events for health workers, linkage between CME and licensing/re-licensing procedures in professional organizations, and provision of competency-based education through work and lifetime, which will influence patients' health outcomes [8, 6, 9, 10].

In Serbia, the movement for continuous quality improvement started with the adoption of system laws in 2005 (Health Care Law, Health Insurance Law, and Law on Health Professional Chambers). These laws also boosted the CME as an integral part of health system development and a necessary condition for the re-licensing of five recognized health professions (physicians, nurses, dentists, pharmacists, and biochemists). To secure a CME of high quality, in 2008, the Health Council of

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Serbia obtained the major role in national accreditation of CME training events [11]. According to the Law on Health Care, the Health Council is a principal advisory body of the Ministry of Health for the long-term planning and development of strategic documents in line with international health policies [12]. Among other activities, Council members perform accreditation of the proposals for continuing education, which is considered an important activity considering the health system development aligned with international and European recommendations. Regarding activities dedicated to CME, the Health Council follows the recommendations and the experience of the European Association of Medical Specialists (UEMS) [13]. The Health Council of Serbia, with the help of chambers, performs reviews of training events following established criteria: evidence-based background of the educational topic, specified target groups, objectives and outcome of training, the existence of before–after knowledge testing and evaluation. Providers of the CME training events come from a broad spectrum of institutions including public and private health organizations, educational institutions, governmental and non-governmental organizations. To keep work license and registration with their chamber, all health professionals are undergoing CME training events every year and must secure the specified number of points per year, which are equal to the duration of several training events.

Building on our first analysis of CME in Serbia in 2015, covering the years 2011 and 2012, we are now in the position to analyze the entire period of seven years from 2011 to 2017 [14]. During this period, the responsible institutions in Serbia (Ministry of Health, Health Council of Serbia, and chambers of regulated health professions) invested much effort to stabilize the system of CME. They followed the Bologna process, the Law on Health Care, the Law on Higher Education in Serbia, and the Strategy for Development of Education in Serbia by 2020 [12, 15, 16]. Furthermore, the Law on Chambers of Health Workforce requests obligatory re-licensing every seven years based on a pre-defined number of CME credits [17]. In 2015, we concluded that medical faculties are best suited to set the standards for CME as far as it is obligatory for medical professionals. The present paper attempts to investigate whether improvements in the organization and practice of CME for physicians can be identified, especially concerning the standards set by the four medical faculties in Serbia.

METHODS

The Health Council of Serbia must approve the continuing education of all health professions, and therefore keeps a comprehensive database. For this study, the Health Council provided the data of 11,557 courses for CME of physicians, submitted between 2011 and 2017. In 2017 alone, reviewers of the Serbian Health Council analyzed 2928 submissions for continuing education of physicians and 2157 for other health professions. (Appendix 1: CME, all health professions, 2017). The number of proposals submitted is almost identical across four cycles, e.g., in 2016 and 2017, with minor variations in the type of proposal. The database for Serbian physicians comprised 26 variables (Appendix 4), thereof six variables are interval-scaled, and 20 are nominal-scaled. We did not further consider the type and number of participants (nine nominal variables) as the latter was not available and the status of accreditation was a nominal process variable of no relevance for this analysis. This leaves us with 16 variables for the analyses.

For the description, we applied the median and interquartile range because of the heterogeneity of the datasets. As many lecturers are repeatedly reading, we count the number of lecturers per course but sum-up across all courses as "lectorates." Due to the predominance of nominal data, we used a principal component analysis (PCA) using a nonlinear iterative partial least squares (NIPALS) algorithm to arrange 16 variables with complete information in such a way that the most influential factors could be displayed and ranked increasing interpretability, but at the same time minimizing information loss. The NIPALS algorithm allows to include nominal data as well. Our findings are underpinned by the in-depth delineation of the outcomes of price patterns and attraction (e.g., hours per credit point). Analyses were done with TIBCO Software [18]. As of January 1, 2011, the national currency of dinar is traded against the euro at a rate of around 118 dinars per euro.

RESULTS

The organizers traditionally submit the most significant number of proposals through the Medical Chamber (2928 proposals in total in 2017), followed by the Nursing and Health Technicians Chamber (1630 in total), the Pharmacy Chamber (226), the Dental Chamber (156), the Chamber of Biochemists (49), and the Health Council – for combined education which includes health professionals of different occupation (96), see Appendix 2: continuing medical education in Serbia, specified by field of education and year. There are four cycles for submissions of proposals per year. The average number of proposals accredited per cycle is 1178 out of the total submitted for accreditation – an average of 1271. Of the total of 5085 proposals for CME accreditation in 2017, after the submission of comments and additions, 92.68% were positively resolved within the observed period of one year. Share of accredited proposals out of the total submitted by chambers is the following: physicians – 96.2%, nurses – 91%, biochemists – 85.7%, pharmacists – 85.4%, dentists – 78.9%, health professionals of other occupation – 55.2%.

In Table 1, a total of 11,557 courses targeted physicians during the period 2011–2017 including 43 courses with incomplete data. They have been classified according to the three main categories of preclinical, clinical, and public health continuing education programs. The Faculty of Medicine of Belgrade takes the top position among the medical faculties in Serbia – which should set the standards – with 569 courses or more than 80 on average per year.

Table 1. Continuing medical education in Serbia, summarized overview of all courses submitted 2011–2017

Field of education	FM Belgrade	FM Novi Sad	FM Kragujevac	FM Nis	Other faculties / educational institutions	Non-educational institutions	Missing Data	Totals including missing data
Pre-clinical	169	28	76	32	107	2290	2	**2704**
Clinical	315	195	179	57	169	5969	20	**6904**
Public health	85	19	12	20	109	1683	3	**1931**
Missing	0	1	0	0	0	17	0	**18**
Totals	**569**	**243**	**267**	**109**	**385**	**9959**	**25**	**11,557**

FM – faculty of medicine

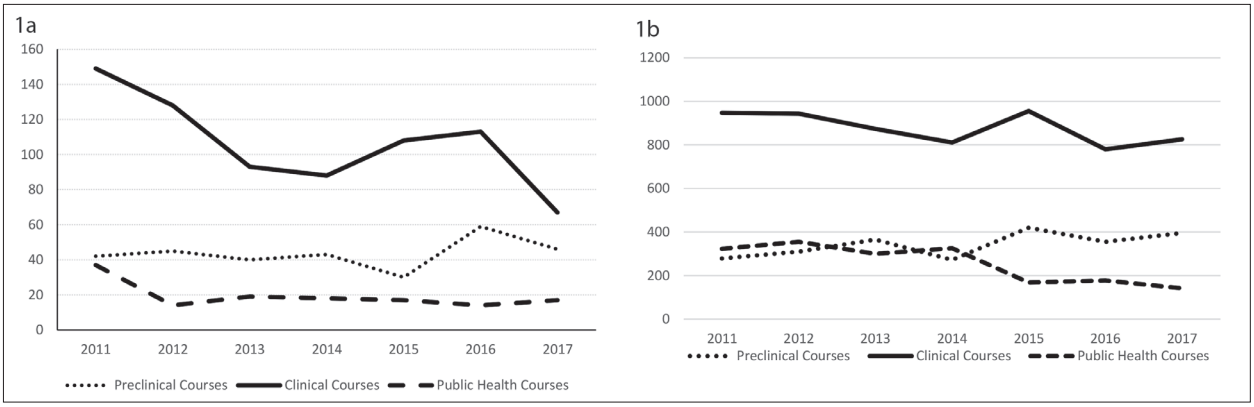

Figure 1a. Continuing medical education offered by the medical faculties of Serbia

Figure 1b. Continuing medical education offered by other providers

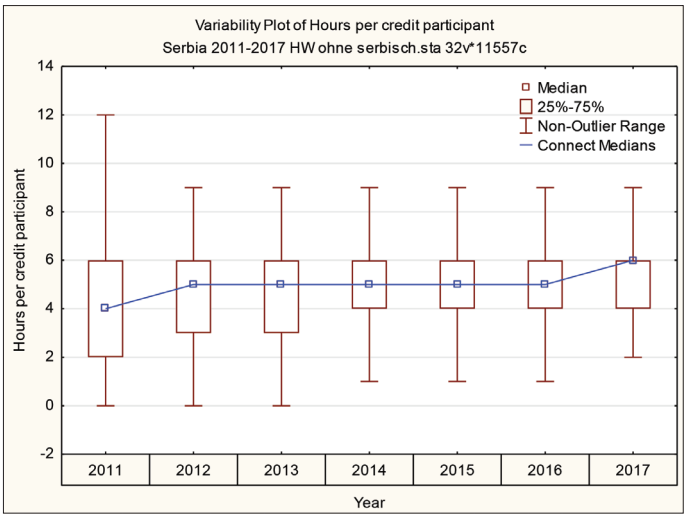

Figure 2. Hours per credit attended 2011–2017

However, far more courses are organized by non-educational institutions like health insurances or non-governmental organizations, with 86.2% of all courses offered (other state health institutions, professional organizations, non-governmental organizations, industry, etc.). Clinical topics dominate the thematic spectrum with 59.7%, followed by pre-clinical topics with 21%, and public health with 19.3%.

Figures 1a and 1b show the development over the years (more details in Appendix 2: continuing medical education in Serbia, specified by field of education and year). There is a negative trend of submitted courses, e.g., for clinical courses offered by the medical faculties (Figure 1a) and similarly for all other providers (Figure 1b). Together, the course portfolio shrinks over the years from the maximum of 1796 in 2012 to 1494 in 2017, i.e., by 16.8%. This trend is the highest for public health with a reduction of 56.9% since the maximum in 2012. The intermediary rise in preclinical courses in 2016 may be due to courses submitted in 2015 and accredited later.

Figure 2 shows the hours attended per rewarded credit point, which demonstrates a remarkable stability of the system in that between 2012 and 2016 the median of required hours per credit remains stable at five hours and the range of hours for 50% of all courses (interquartile range) remains stable between four to six hours for the period between 2014 and 2017.

Regarding the prices per course participant, Figure 3, in general, shows the highest prices for Belgrade. The differences between Belgrade and Central Serbia as well as between Central Serbia and Vojvodina across the fields of education are significant (ANOVA based on means: $p < 0.001$).

To understand data better, Figure 4 shows a breakdown by the responsible four medical faculties and the remaining groups of other educational and non-educational institutions. Between 2011 and 2017, the medical faculties ask for the highest prices, especially the Faculty of Medicine in Niš, in the field of public health. Also, Novi Sad and Belgrade stand out for the clinical field of education.

To determine the relevance of the 16 variables with complete and relevant information available, we performed a PCA. The PCA identified eight variables as important,

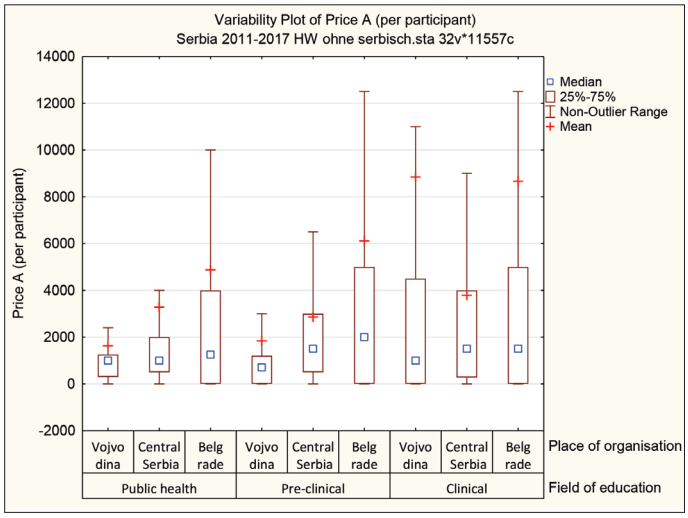

Figure 3. Comparison of prices per hour by field of education and province of Serbia 2011–2017

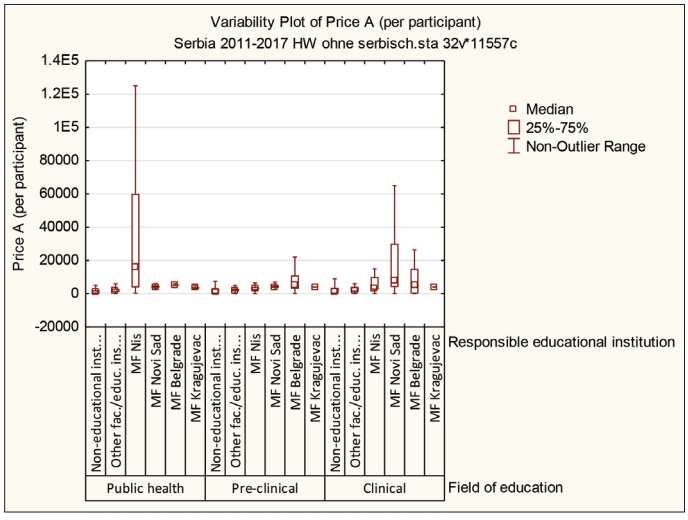

Figure 4. Breakdown of prices by the responsible institution

scaled according to what is usually known as 'Power,' a quantity ranging 0–1.

Variables with high power (≥ 0.99):

1. Duration of education (hours)
2. Credit points for lecturers
3. Hours per credit lecturer
4. Price per participant
5. Number of domestic lecturers
6. Number of international lecturers
7. Hours per credit participant
8. Credit points for participants.

The eight variables out of 16 available that are not well represented (i.e., have low values of power) are more likely to be unimportant (for details see Appendix 3 – principal component analysis).

DISCUSSION

Despite their minor quantitative contribution to CME in Serbia, medical faculties should be the ones to initiate urgently required improvements of the entire system, due to their societal lead role in education and science, whereas e.g., Maisonneuve et al. [19] found that pharmaceutical industry accounts for more than 50% of CME in five European countries, financing and stabilizing the existing system. This may also explain the relative stability of public health related courses offered by medical faculties, whereas those offered by other providers show a clear downward trend (Figures 1a and 1b). On the other hand, clinical topics offered by academic providers trend downwards whereas the number of courses offered by non-academic providers is rather stable, at least over the last years. In this regard, it is regrettable that the numbers of course participants (course attendance) are not available. This would allow to analyze whether increased participation per course compensates for the lesser number of courses offered, although this may be considered rather unlikely.

As demonstrated in Figures 1a and 1b, the system is stable, but at a standstill or even a slightly downward trend it is visible in the number of courses. The PCA identified duration, credit points, price, and number of lecturers, and thereby determined the variation presented in Figures 1–4. Modifying these parameters has the potential to adapt the profile better to needs. These critical issues have to be discussed between the providers and the accrediting Health Council of Serbia to analyze the areas of possible improvement. The steep downward trend for CME in public health may also be due to the deficit in up-to-date teaching material, which since the end of the European Stability Pact and the 2nd edition of the Programmes for Training and Research in Public Health in 2013 [20] has not been updated in spite of the positive experience summarized by Zaletel-Kragelj et al. [21].

Recent publications on CME are rare; at the end of 2009, Garattini et al. [22] published an analysis of six European countries, which revealed different models regarding compliance, financial incentives for some categories of physicians, formal accreditation of providers, and private sponsorship. Regulatory bodies exist in some countries (e.g., Germany and the United Kingdom – UK), whereas self-regulation is considered sufficient to secure high quality care in, e.g., Austria and Spain [23].

A model for progressive change is provided by recent developments in the UK initiated by the report on "Unfinished Business" published in 2002 [24, 25]. A so-called 'gold guide' was first published in 2010 (sixth edition 2016), providing a reference to postgraduate training in the UK [26]. The following improvements are also especially relevant for Serbia:

- Provision of a more standardized national program also for the entry into CME in which all trainees must achieve a standardized list of generic competencies (not yet available in Serbia);
- Promotion of the concept of work-based and competency-based assessment and feedback.

Since 2010, only one organization, the General Medical Council (GMC), oversees an integrated under- and postgraduate education in the UK [27, 28], which is the same as in Serbia, as only the Serbian Health Council supervises the process; however, the precise criteria for supervision are still not endorsed. An example of good practice in the UK is the "framework for the Professional Development of Postgraduate Medical Supervisors," established as early as 2009 [29]. Analogous concepts are promoted in the United States [30]. In the Netherlands, VanNieuwenborg et al. [31] argue that "CME should go beyond the sheer acquisition of knowledge, and also seek changes in practice, attitudes and behaviors of physicians." With the same intention, Whitehurst [32] asks for a "continuing medical education partnership." A related model to involve practice experience as an essential element in CME has been proposed by Wiese et al. [33].

The analysis of the period 2011–2017 and the published literature during the last five years confirm the recommendations published in 2015 [14, 22, 23, 24, 26, 28–33]:

Administrative organization

1) Improve the database quality of the national registration especially to include data on final delivery; 2) Providers should rigorously follow their obligation to produce evaluation reports after completion of educational events, to the appropriate chamber and to the Health Council; 3) Limit the course fee rates per hour; 4) Reduce the percentage of obligatory payments to the administration and arrange for a cheaper production of certificates in order to save money for remuneration; 5) Request lecturing in CME programs of the faculties of medicine as obligatory for academic promotion together with an increase of remuneration. The Faculty of Medicine in Belgrade has adopted these standards already.

Innovative development

1) Going online towards blended learning; 2) Adopt best practice from a competitive market; 3) Increase attractiveness for participants from South-Eastern Europe (especially from the former Yugoslavia) and from abroad in general (if English speaking); 4) Invest in bilateral agreements with big organizations; 5) Organize focused publicity.

CONCLUSION

Integrated education including practice experience is a key element to improve CME in Serbia. To follow-up on this process there should certainly be more rigid control of submitted courses by the Health Council of Serbia regarding the timeliness of submissions, the completeness of data, and the reporting of delivered CME. The key determinants of change should be adapted accordingly as there are duration, credit points, price, and number/variety of lecturers.

The Faculty of Medicine of Belgrade has invested considerable effort to stabilize and further develop the system of CME between 2013 and 2017, and these standards should be enforced nation-wide for all providers. Reorganization and adaptation to a changing environment become mandatory if stagnation and outclassing of CME should be avoided.

Conflict of interest: None declared.

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Стагнација континуиране медицинске едукације у Србији у периоду 2011–2017. године

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САЖЕТАК

Увод/Циљ Континуирана медицинска едукација (КМЕ) пресудан је елемент за одржавање нивоа професионалности у три кључне области медицинског образовања: преткличничком, клиничком и јавном здрављу. Профил КМЕ у Србији анализиран је у периоду 2011–2017. године.

Методе У периоду 2011–2017. године предато је на акредитацију 11.557 едукација КМЕ, које су описане са 26 променљивих. Због превладавања номиналних података користили смо анализу главних компонената помоћу алгоритма *NIPALS* да бисмо 16 променљивих (варијабли) поређали са потпуним информацијама на такав начин да се најутицајнији фактори могу приказати и рангирати. Анализа је урађена са статистичким софтвером *TIBCO*.

Резултати Медицински факултет у Београду заузима водеће место међу медицинским факултетима у Србији са 569 курсева или 47,9% (n = 1187; 2011–2017), док су необразовне установе са 86,2% (n = 11.514) најдоминантније у организацији КМЕ курсева (као пружаоци услуга КМЕ). Клиничке области доминирају са 59,7%. Између 2012. и 2017. године укупан број курсева се смањио за 16,9%. Од 16 могућих детерминанти КМЕ, према анализи главних компонената, најрелевантније су трајање, број добијених бодова, цена и број предавача.

Закључак Током последње деценије може се уочити застој или чак назадовање у развоју. Посебно би медицински факултети у Србији, као и други значајни организатори (пружаоци услуга), требало да преиспитају целокупну структуру своје административне организације и покрену иновативни развој.

Кључне речи: континуирана медицинска едукација; акредитација; евалуација; медицински факултети; Србија

Appendix 1. Continuing medical education, all health professions, 2017

Total continuing medical education accreditation results for four cycles (January 2017, April 2017, Jul 2017, October 2017)

Chamber	Professional meetings		Courses and seminars		Congresses/ symposiums		On-line testing		Total proposals submitted	Total complains submitted	Complains positively solved	Total accredited
	S	R	S	R	S	R	S	R				
Physicians	1493	72	683	77	239	10	305	49	2928	147	98	2818
Nurses	910	115	232	37	51	4	249	32	1630	88	42	1484
Pharmacists	105	19	44	3	3	/	29	23	226	13	12	193
Dentists	25	9	27	11	35	2	32	15	156	4	4	123
Biochemists	33	2	5	/	2	/	/	7	49	2	2	42
Health professionals of other occupation	15	32	19	11	10	4	/	5	96	14	9	53
Total	**2581**	**249**	**1010**	**139**	**340**	**20**	**615**	**131**	**5085**	**268**	**167**	**4713**

S – submitted; R – refused as not appropriate;
Note: Success of accreditation – share of accredited proposals in total submitted

Appendix 2. Continuing medical education (CME) in Serbia, specified by field of education and year

Field of CME	Faculty of Medicine, Belgrade (FMB)	All 4 medical faculties (incl. FMB)	All other organizers	TOTALS (%)
2011				
Preclinical	19	42	279	321 (18.06)
Clinical	61	149	947	1096 (61.68)
Public Health	14	37	323	360 (20.26)
TOTAL 2011	94	228	1549	1777
2012				
Preclinical	24	45	310	355 (19.77)
Clinical	45	128	944	1072 (59.69)
Public Health	8	14	355	369 (20.55)
TOTAL 2012	77	187	1609	1796
2013				
Preclinical	23	40	365	405 (23.95)
Clinical	39	93	874	967 (57.19)
Public Health	12	19	300	319 (18.86)
TOTAL 2013	74	152	1539	1691
2014				
Preclinical	27	43	272	315 (20.22)
Clinical	41	88	811	899 (57.70)
Public Health	11	18	326	344 (22.08)
TOTAL 2014	79	149	1409	1558
2015				
Preclinical	19	30	420	450 (26.49)
Clinical	49	108	956	1064 (62.63)
Public Health	17	17	168	185 (10.89)
TOTAL 2015	82	155	1544	1699
2016				
Preclinical	27	59	355	414 (27.62)
Clinical	40	113	780	893 (59.57)
Public Health	11	14	178	192 (12.81)
TOTAL 2016	78	186	1313	1499
2017				
Preclinical	30	46	396	442 (29.59)
Clinical	40	67	826	893 (59.77)
Public Health	15	17	142	159 (10.64)
TOTAL 2017	85	130	1364	1494
2011-2017				
Preclinical	169	305	2397	2702 (23.47)
Clinical	315	746	6138	6884 (59.79)
Public Health	85	136	1792	1928 (16.74)
TOTAL 2011–2017	569	1187	10,327	11,514

Note: Courses with incomplete data are excluded (n = 43)

Appendix 3. Principal component analysis (variables with a power ≥ 0.99 are in bold)

Variable	Variable importance (Serbia 2011–2017) Number of components is 7			Variable group	
	Variable number	Category value	Power	Importance	
Type of education {international conference}	1	3	0.319052	15	1
Type of education {national courses}	1	2	0.270487	16	
Type of education {national conference}	1	4	0.198262	19	
Type of education {international courses}	1	1	0.067256	25	
Field of education {public health}	2	3	0.017893	38	
Field of education {clinical}	2	2	0.016812	39	
Field of education {pre-clinical}	2	1	0.012881	41	
Organizational level of organizing institution {health care system / broader system / educational system}	3	5	0.655928	12	1
Organizational level of organizing institution {tertiary health care}	3	3	0.254120	17	
Organizational level of organizing institution {primary health care}	3	1	0.115224	21	
Organizational level of organizing institution {several levels combined}	3	4	0.090667	24	
Organizational level of organizing institution {secondary health care}	3	2	0.044299	29	
Organizer of education {NGO}	4	6	0.948278	10	1
Organizer of education {health institute}	4	4	0.220569	18	
Organizer of education {clinical center}	4	2	0.144493	20	
Organizer of education {faculty or other educ. institution}	4	1	0.095727	22	
Organizer of education {PHC}	4	5	0.064331	26	
Organizer of education {other inst. of nat. interest}	4	7	0.042038	30	
Organizer of education {gen. hospital / spec. hospital}	4	3	0.040430	31	
Responsible educational institution {non-educational institution}	5	6	0.095597	23	1
Responsible educational institution {FM Belgrade}	5	1	0.036176	32	
Responsible educational institution {FM Novi Sad}	5	2	0.026819	34	
Responsible educational institution {FM Kragujevac}	5	3	0.020710	37	
Responsible educational institution {other fac./educ. institution}	5	5	0.014485	40	
Responsible educational institution {FM Niš}	5	4	0.009202	43	
Status of course organizer {NGO}	6	4	0.949097	9	1
Status of course organizer {state inst.}	6	1	0.811897	11	
Status of course organizer {private inst.}	6	3	0.029601	33	
Status of course organizer {military inst.}	6	2	0.007268	44	
Organization of course {In cooperation with others}	7	2	0.026309	35	
Organization of course {one organizer}	7	1	0.026010	36	
Organization of course {11}	7	11	0.000304	46	
Place of organization {Central Serbia}	8	3	0.054656	27	1
Place of organization {Belgrade}	8	2	0.050961	28	
Place of organization {Vojvodina}	8	1	0.010875	42	
Number of domestic lecturers	**9**		**0.999981**	**5**	**1**
Number of international lecturers	**10**		**0.999749**	**6**	**1**
Credit points for lecturers	**20**		**1.000000**	**3**	**1**
Credit points for participants	**21**		**0.991099**	**8**	**1**
Duration of education (hours)	**22**		**1.000000**	**1**	**1**
Status of accreditation {reapplication}	23	2	0.625976	13	1
Status of accreditation {accepted with remark}	23	3	0.582916	14	1
Price per participant	**24**		**1.000000**	**2**	**1**
Hours per credit lecturer	**30**		**1.000000**	**4**	**1**
Hours per credit participant	**31**		**0.991428**	**7**	**1**
Number of variable groups included					16

NGO – non-governmental organization; PHC – primary health care; FM – faculty of medicine

Appendix 4. List of variables provided

No.	Name of variable
1	Type of education
2	Field of education
3	Organizational level of organizing institution
4	Organizer of education
5	Responsible educational institution
6	Status of course organizer
7	Organization of course
8	Place of organization
9	Number of domestic lecturers
10	Number of international lecturers
11	Type of participants
12	Physicians
13	Dentists
14	Pharmacists
15	Biochemists
16	Nurses
17	Technicians
18	Others
19	Number of participants
20	Credit points for lecturers
21	Credit points for participants
22	Duration of education (hours)
23	Status of accreditation
24	Price A (per participant)
25	Price B
26	Year

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

COVID-19 pneumonia complicated by late presentation of bilateral spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema

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SUMMARY

Introduction Over the last few months the coronavirus disease 2019 (COVID-19) pandemic has created overwhelming challenges for physicians around the world. While much has been described in the literature about lung infiltrates and respiratory failure associated with infection of coronavirus 2 (SARS-CoV-2), pneumothorax is reported as a rare (a rate of 1%) but a life-threatening complication of COVID-19 pneumonia. Late bilateral spontaneous pneumothorax has been described in few cases. The aim of the report is to consider pneumothorax as a possible complication of COVID-19 pneumonia, which is also one of the causes of respiratory deterioration and potentially fatal outcome in these patients.

Case outline This article describes the clinical course of the patient who tested positive for SARS-CoV-2 on reverse-transcriptase polymerase chain reaction (RT-PCR) testing of nasopharyngeal and oropharyngeal swab specimens and who presented with COVID-19 pneumonia complicated by bilateral, spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema. He had no underlying lung disease nor risk factors for pneumothorax, except administered non-invasive ventilation/continuous positive airway pressure during first hospitalization. The patient was successfully treated with surgical (chest drainage, thoracoscopy and pleural abrasion) and non-surgical methods (by application of drugs and other supportive therapies).

Conclusion This review demonstrates that the possibility of a late pneumothorax should be kept in mind in patients with, or recovering from, COVID-19 disease with progressive dyspnea. The timely diagnosis and management of pneumothorax will reduce COVID-19 associated mortality.

Keywords: COVID-19; complications; management

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been recognized as a worldwide pandemic [1]. COVID-19 is a systemic infectious disease. This infection has a broad spectrum of presentations that can range from asymptomatic disease to fatal acute respiratory distress syndrome (ARDS) with death due to multi-organ failure [2].

Initial chest X-ray (CRX) may be normal but patients may later develop radiological signs of COVID-19 pneumonia. In critically ill patients with marked respiratory symptoms, CRX can be diagnostic for COVID-19 pneumonia. Some patients with PCR confirmed COVID-19 infection had changes on initial computed tomography (CT) and radiographs were false negative. Therefore, these imaging methods can help both in diagnosis and in the management of COVID-19 patients [3, 4].

The important causes of sudden respiratory deterioration associated with COVID-19 pneumonia are ARDS, pulmonary embolism and pneumothorax. They need a prompt diagnosis and intervention in order to reduce COVID-19 associated mortality [5, 6]. The aim of the report is to consider pneumothorax as a possible complication of COVID-19 pneumonia, which is also one of the causes of respiratory deterioration and potentially fatal outcome in these patients.

CASE REPORT

We report a case of a 47-year-old white male with no history of pulmonary disease, nonsmoker, weightlifter (BMI 30.7), who presented with symptoms of muscle and joint pain, malaise, and hemoptysis five days prior to hospitalization. On admission day, he developed a fever up to 38°C (100.4°F) and dyspnea. CRX revealed signs of bilateral pneumonia, O2 saturation 94%, heart rate 80/minute, leucopenia 3.06 × 109 and C-reactive protein 65.7 mg/L. Nasopharyngeal and oropharyngeal swab for COVID-19 PCR testing were positive. On the second day of hospitalization, he was transferred to Intensive care unit (ICU) due to respiratory failure, where non-invasive ventilation/continuous positive airway pressure was administered. After detection of high levels of

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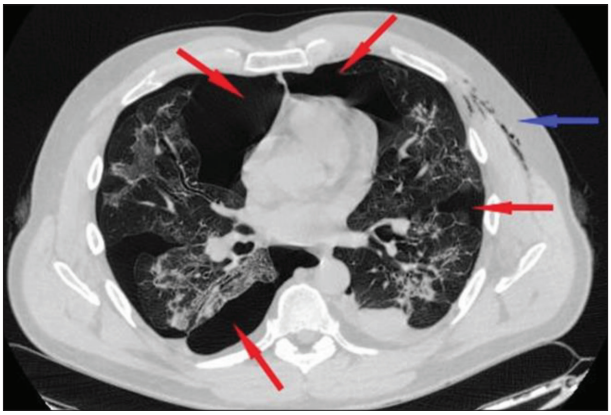

Figure 1. Chest computed tomography scan on admission; red arrows show bilateral pneumothorax; blue arrow shows subcutaneous emphysema

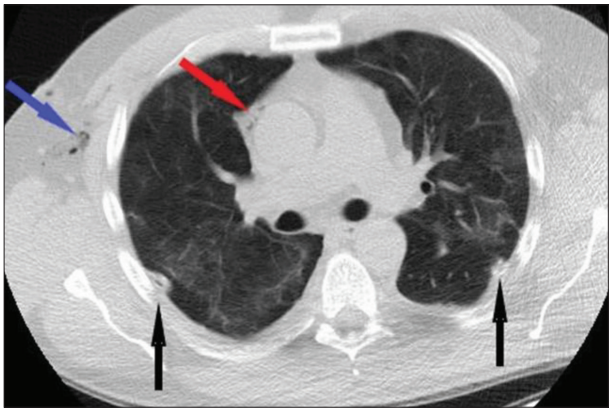

Figure 2. Chest computed tomography scan after bilateral chest tube placement; black arrows show chest tubes; the blue arrow shows subcutaneous emphysema; the red arrow demonstrates the Macklin effect

IL-6, tocilizumab was administered during the second and third day of ICU treatment in doses of 8 mg/kg. Total length of ICU treatment was 10 days. After stabilization of respiratory function (arterial SO_2 98% on 4/L min of O_2) COVID-19 PCR testing was repeated negative in two samples. During the hospitalization he was treated with dexamethasone 6 mg/24h for 10 days. Piperacillin/tazobactam was discontinued on the 14th day. On the 20th day of hospitalization, severe dyspnea was reported with CRX showing signs of complete left sided pneumothorax. Chest tube No. 22F was inserted and connected to water seal and active suction of -20 cm H_2O. After placement of chest tube there were no signs of air leak, so the drain was removed on the fifth day after placement, with fully expanded lungs on CRX. He was discharged after 25 days of hospitalization.

The day after he was discharged, the patient developed signs of severe dyspnea. Chest CT showed complete bilateral pneumothorax (Figure 1).

After admission to the thoracic surgery clinic, bilateral chest drainage was performed with 22F chest tubes. The chest tubes were connected to water seal and active suction -20 cm H_2O with severe bilateral air leakage and hemorrhagic secretion up to 200 ml/24h in combination with necrotic detritus. Initial CRX after drainage showed complete lung expansion. Due to the prolonged air leak on the right chest drain, control chest CT was performed on day 11 of admission (Figure 2).

CT described a full expansion of the left lung, partial right sided pneumothorax, subcutaneous emphysema, mediastinal Maclin effect and signs of bilateral ground glass opacity in regression. The left chest tube was clamped for 24 hours on day 12 after no signs of air leak was present for three days. Left sided chest tube was removed on day 13. Right sided chest tube was connected to Medela Thopaz pump -2kPa (Medela HQ., Baar, Switzerland) with air loss measuring in range from 10–80 ml/min. On day 15, the air leak stopped, but CRX showed signs of complete right sided pneumothorax. Inactive right sided chest tube, blocked with necrotic detritus, was removed and drainage was performed with chest tube No. 24F. Due to the prolonged and severe air leak after the drainage, accompanied

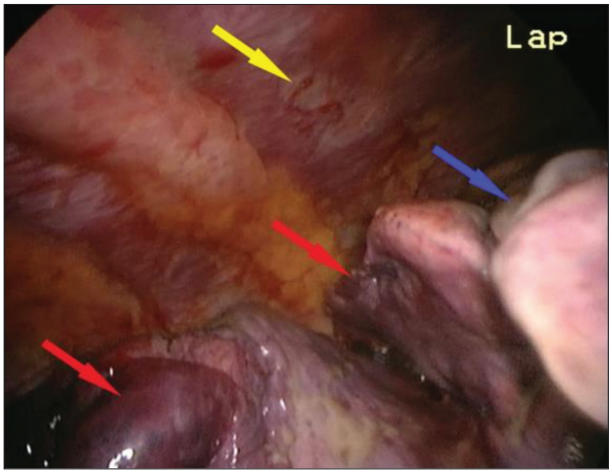

Figure 3. Video-assisted thoracoscopic surgery procedure; red arrows show necrotic posteriors segments with bullae; the blue arrow shows fibrin deposits on visceral pleura; the yellow arrow shows inflamed parietal pleura

with the complete lung collapse on CRX, the patient was operated in general anesthesia on day 15 of hospitalization. Uniportal right sided video-assisted thoracoscopic surgery was performed. During the operation signs of partial necrosis of S2, S6, and S8–10 lung segments were detected, with fibrin deposits on visceral pleura (Figure 3).

No obvious spots of air leak were detected. Complete abrasion of parietal pleura was performed with placement of two chest tubes No. 28F. Samples of parietal pleura were sent to pathophysiology: acute purulent inflammation of the pleura. On the first postoperative day there were no signs of air leak. CRX showed fully expended lungs. On the seventh postoperative day one chest tube was removed. The following day the second chest tube was clumped for 24 hours. CRX showed signs of full lung re-expansion, so the following day the last chest tube was removed. He was discharged after 25 days of rehospitalization.

Three months after discharge control chest CT was performed (Figure 4): No signs of pneumothorax and pneumomediastinum. Complete regression of ground-glass opacification with few reticular intestinal lesions in regression. SARS-CoV-2 IgM and IgG antibodies were present.

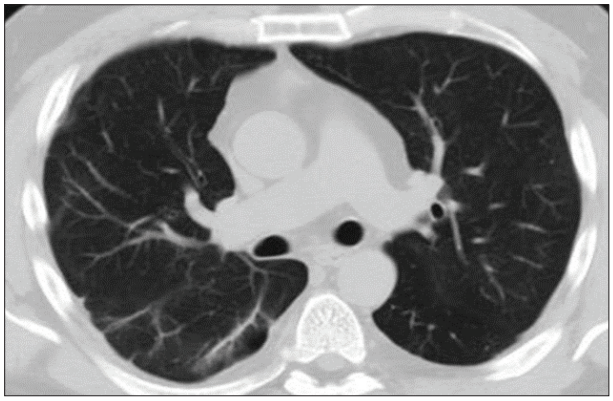

Figure 4. Control chest computed tomography scan three months after discharge

Written consent to publish all shown material was obtained from the patient.

DISCUSSION

Radiology frequently shows typical changes of COVID-19 pneumonia [4]. Chen et al. [7] first reported pneumothorax as a rare radiologic feature in 1% of patients with COVID-19. Late bilateral spontaneous pneumothorax has not yet been widely reported in the literature [6, 8]. Patients can develop pneumothorax at different stages of the COVID-19 disease course [9]. It is important to consider the diagnosis of pneumothorax in COVID-19 patients, if there is a sudden increase in work of breathing, decreased oxygen saturation, or the patient complains of chest tightness. In case of sudden deterioration, urgent CRX, ultrasound or computed topography scan should be done, and expert help sought [6, 7, 8].

Like many other authors, we believe that the combination of severe inflammation and prolonged duration of illness in COVID-19 patients contributed to the pulmonary parenchymal injury (degenerative changes in the lung parenchyma) in patients with the development of air leaks leading to pneumothorax, and/or pneumomediastinum, and subcutaneous emphysema [10, 11, 12]. The lungs of patients with COVID-19 who have significant interstitial involvement appear physiologically small, with low compliance and reduced elasticity. This thickened, stiff tissue makes it difficult for the lungs to work properly, and sustained-pressure ventilation may be necessary to obtain acceptable gas exchanges. In this setting, parenchyma is prone to rupture, with consequent risk of pneumothorax [10]. In some cases, progression to ARDS causes diffuse alveolar damage and a pro-inflammatory cytokine storm, which can induce alveolar rupture and the development a new lesion - pneumatoceles and pneumothorax [13, 14]. Likewise, severe airway inflammatory damage from the release of cytokines in COVID-19 can lead to weakening of the bronchial walls [15].

The most common causes of pneumothorax in respiratory infection have been associated with barotraumas in mechanically ventilated patients or increased airway pressure due to ARDS. Pneumothoraxes that developed in patients with COVID-19 and ARDS have been attributed to the same etiologies [5, 16]. Endotracheal intubation and mechanical ventilation are known to cause iatrogenic pneumomediastinum, subcutaneous emphysema, and pneumothorax [5, 16]. Our patient did not have ARDS based on criteria and was not intubated. He developed both a severe pneumonia and unilateral pneumothorax, and later in the course of the disease bilateral pneumothorax, which may be a consequence not only of COVID-19 pneumonia, but also as a consequence of non-invasive ventilation/continuous positive airway pressure application. Although pneumothorax can be a complication of positive airway pressure in patients with ARDS receiving mechanical ventilation, most of the COVID-19 patients, did not receive any form of ventilation pneumothorax [5]. The diffuse alveolar damage seen in both ventilated and unventilated COVID-19 patients may cause development of bullae and create predisposition for pneumothorax in different stages of disease [5, 9, 17].

The pathogenesis of pneumomediastinum follows the so-called "Macklin effect". The Macklin effect seen on thoracic CT suggests that air leakage is caused by rupture of the alveoli and rupture of the mediastinal pleural traces along the broncho-vascular sheath to the mediastinum, and then to the subcutaneous tissue and in the pleural space. This is likely to happen in patients with COVID-19 due to cough, which is known to increase intra-alveolar pressure [18].

The appearance of pneumothorax in patients with COVID-19 pneumonia might be caused by underlying pulmonary diseases. Patients with chronic obstructive pulmonary disease and pulmonary emphysema are at higher risk of pneumothorax when infected with SARS-CoV-2 [19]. Signs suggestive of potential comorbidities on CRX might be obscured by signs of COVID-19 pneumonia [20]. However, in some cases, COVID-19 pneumonia changes might be so widespread that features suggestive of comorbidities are obscured.

It was found that pneumothorax can occur in patients with COVID-19 pneumonia without preexisting lung disease [12]. Our patient did not have a history of pneumothorax, underlying pulmonary disease and had no history of smoking. Therefore, it is our opinion that the development of these pneumothoraxes are results of advanced alveolar damage, bronchiolar distortion leading to pulmonary bullae formation and tissue necrosis, predominantly of posterior lung segments. Moreover, the severe cough associated with viral infections increases the intrapulmonary pressure. This may precipitate bullae rupture and pneumothorax formation [18].

When pneumothorax occurs in COVID-19 patients, chest drainage represents first-line of treatment [21]. Managing pneumothorax in these patients is crucial to prevent the development of life-threatening tension pneumothoraxes. We note that the initial treatment of unilateral pneumothorax with a tube thoracostomy provided a satisfactory but temporary outcome, most likely due to massive pulmonary changes in our patient. It is our belief

that the final outcome of pneumothorax in patients with COVID-19 pneumonia depends on the severity (and progression) of lung disease, and therefore prompt surgical treatment of pneumothorax in these patients provides appropriate outcomes. The patient was treated with steroid therapy based on institutional policy for severe disease. Therefore, we believe that the use of drugs and other supportive therapies has also contributed to a favorable treatment outcome. After chest tube placement, a wait-and-see strategy was preferred over the aggressive pleurectomy or pleural abrasion because of doubts about the effectiveness of the procedure. However, in case of persistent or repeating pneumothorax, thoracoscopy and pleurectomy/pleural abrasion or even apical blebs resection (when present) can be feasible options to reduce air leakage and improve ventilation [21, 22]. The ideal timing of minimally invasive treatment (video-assisted thoracoscopic surgery) is unclear. Even in cases of repeated and persistent pneumothorax in patient with COVID-19 pneumonia, we recommend delaying thoracoscopic operative management in the light of uncertain course of the disease and potential progression of lung tissue damage. While operative management in this patient had a good outcome, it seems that prolonged management with chest tubes is needed for resolution of air leaks from injured and fibrotic pulmonary parenchyma.

The worsening status of patients infected with SARS-CoV-2 should not always be attributed to disease progression, but also pneumothorax. Early diagnosis and timely treatment of this complication can improve the therapeutic effect and reduce mortality [23].

Conflict of interest: None declared.

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Упала плућа изазвана болешћу *COVID-19* која је компликована касном појавом обостраног спонтаног пнеумоторакса, пнеумомедиастинума и поткожног емфизема

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САЖЕТАК

Увод Током последњих неколико месеци пандемија болести изазване вирусом корона 2019 (*COVID*-19) створила је велике изазове за лекаре широм света. Иако је у литератури много писано о плућним инфилтратима и респираторној инсуфицијенцији који су у вези са инфекцијом вирусом корона 2 (*SARS-CoV*-2), пнеумоторакс је пријављен као ретка (стопа од једног процента) али по живот опасна компликација болести *COVID*-19. Касна појава обостраног пнеумоторакса описана је у само неколико случајева.

Циљ приказа је да се размотри пнеумоторакс као могућа компликација упале плућа изазване болешћу *COVID*-19, који је и један од узрока респираторног погоршања и могућег смртног исхода код ових болесника.

Приказ болесника Чланак описује клинички ток болесника чији је брис назофаринкса и орофаринкса испитиван методом *RT-PCR* био позитиван на *SARS-CoV*-2. Он је развио упалу плућа изазвану болешћу *COVID*-19 која је компликована обостраним, спонтаним пнеумотораксом, пнеумомедиастинумом и поткожним емфиземом. Болесник није имао ранију болест плућа нити факторе ризика за пнеумоторакс, осим примене неинвазивне вентилације/континуираног позитивног притиска у дисајним путевима током прве хоспитализације. Успешно је излечен хируршким (дренажом грудног коша и торакоскопском абразијом плућне марамице) и нехируршким методама (применом лекова и других супортивних мера).

Закључак Овај случај показује да треба имати на уму могућност пнеумоторакса код болесника са болешћу *COVID*-19 и оних у фази опоравка од болести а који имају прогресивну диспнеју. Правовремена дијагностика и лечење пнеумоторакса може да допринесе смањењу морталитета који је у вези са болешћу *COVID*-19.

Кључне речи: *COVID*-19; компликације; лечење

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Spontaneous coronary artery dissection as a cause of acute myocardial infarction with ST elevation

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SUMMARY

Introduction Spontaneous coronary artery dissection (SCAD) is defined as a dissection that has not occurred with atherosclerosis, trauma, or has not developed iatrogenically.

Case outline A 53-year-old man was admitted to the hospital due to chest pain and ischemic electrocardiographical changes. Coronarography was performed and 85% of the stenosis of the first diagonal branch (D1) was registered. During percutaneous coronary intervention (PCI), one drug-eluting was directly implanted into the D1. About three hours after the intervention, the patient developed an acute myocardial infarction with ST elevation (STEMI) and recoronarography was performed. The previously implanted stent in D1 was patent without thrombi. The subocclusive stenosis of the left anterior descending artery (LAD) was registered and PCI was performed. After implantation of the stents into the LAD, propagation of dissection towards left circumflex artery (LCx) was creating significant stenosis. Following the registration of the stenosis, PCI was performed on this branch. In order to determine the cause of acute STEMI, intravascular imaging was performed, seven days after last PCI. Optical coherence tomography showed an excellent stent apposition and expansion. In the area under the stents, in the proximal segment of LAD and LCx, showed duplication in the blood vessel wall. This duplication represents an unresorbed intramural hematoma as a consequence of SCAD.

Conclusion When performing coronarography on younger patients, on women in the peripartum and on patients with connective tissue, SCAD disorders should be kept in mind. The use of intravascular imaging could reduce the number of unrecognized SCAD.

Keywords: spontaneous coronary artery dissection; acute myocardial infarction with ST elevation; optical coherence tomography

INTRODUCTION

Spontaneous coronary artery dissection (SCAD) represents a dissection that occurred without atherosclerosis, trauma or has not developed iatrogenically. There are two theories which describe how SCAD develops [1, 2]. According to the first theory, endothelial injury is accompanied by consequent penetration of blood, into the blood vessel wall [1]. According to the second theory, the primary event is the spontaneous bleeding from the vasa vasorum into the blood vessel wall [2]. SCAD causes 1–4% of all acute coronary events [3]. However, the true incidence and prevalence of SCAD are unknown, because they are often unrecognized. SCAD most commonly occurs in patients who do not have traditional risk factors for cardiovascular diseases [4]. The association with female sex, pregnancy, and oral contraceptives has been described [4, 5]. Systemic arteriopathies are also a predisposing factor and SCAD is most commonly associated with fibromuscular dysplasia. The trigger for the development of SCAD can be intense physical and emotional stress. The first step in the diagnostic algorithm is coronarography, which should be carefully performed to avoid the extension of dissection. In uncertain cases, intracoronary imaging may be helpful.

We present a case of a patient who developed acute myocardial infarction as a consequence of spontaneous dissection of the left anterior descending (LAD) branch of the left coronary artery.

CASE REPORT

A 53-year-old man was admitted to the emergency department due to chest pain and ischemic electrocardiographical (ECG) changes. Cardiovascular risk factors (smoking and obesity) were present, while physical examination did not show any irregularities. Electrocardiogram showed negative T wave in DI, aVL and V5–V6. High-sensitivity troponin was within the reference values. Transthoracic echocardiography initially and after transpulmonary contrast agent administration (Optison; GE Healthcare, Chicago, IL, USA) showed reduced systolic function with regional wall motion abnormalities (medio-apical segments of antero-lateral wall). Dual antiplatelet therapy per protocol for acute coronary syndrome was administered. Coronarography was performed and 85% stenosis of the first diagonal branch (D1) was registered (Figure 1A), while other coronary arteries were without

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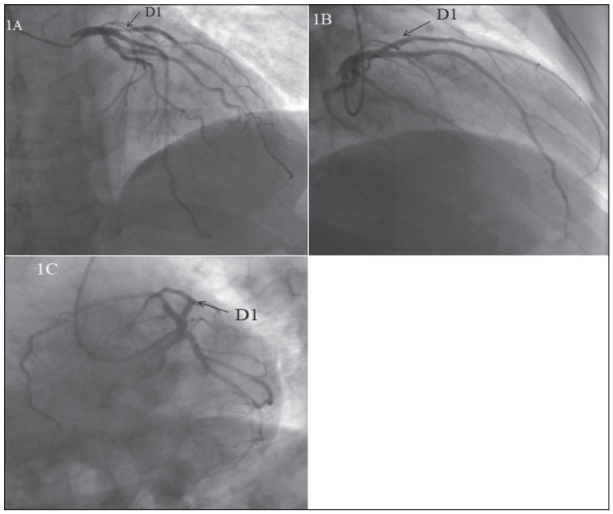

Figure 1. A: Significant stenosis of the first diagonal branch; B: the angiographic result after stent implantation on the first diagonal branch; C: the angiographic result after stent implantation on the first diagonal branch

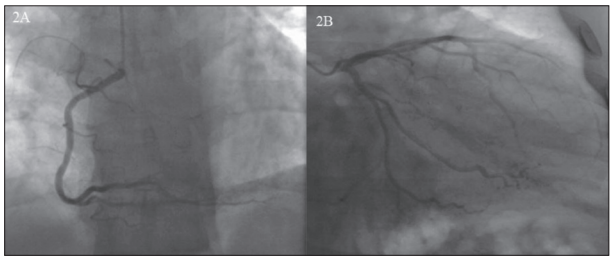

Figure 2. A: There is no significant stenosis on the right coronary artery; B: there is no significant stenosis on the left circumflex coronary artery

significant stenosis (Figures 2A and 2B). During percutaneous coronary intervention (PCI), one drug-eluting stent of 15 × 3.5 mm (XienceXpedition; Abbott Laboratories, Chicago, IL, USA) was directly implanted into the D1 (Figures 1B and 1C). About three hours after the intervention, the patient developed chest pain. On electrocardiogram, ST segment elevation V1–V5 was registered (Figure 3). Because the patient had cardiac decompensation, he was sedated, endotracheally intubated, and invasively mechanically ventilated. Due to suspected acute stent thrombosis, urgent recoronarography was performed, which showed patent previously implanted stent in D1, without thrombi (Figure 4A). However, a subocclusive stenosis was registered in the medial segment of the LAD, approximately 3.5 cm distal to the origin of the first diagonal branch (Figure 4A). During the PCI, two drug-eluting 28 × 3 mm and 28 × 3.5 mm stents (Synergy, Boston, MA, USA) were implanted, with the overlap technique, in the LAD, with optimal angiographic result (Figure 4B). After implantation of the stents into the LAD, significant stenosis of the circumflex branch of the left coronary artery (LCx) was registered (Figure 4B). This stenosis had not appeared during the previous coronarography and was not due to spasm. Drug-eluting 15 × 3 mm stent (Resolute; Medtronic, Dublin, Ireland) was implanted into the proximal segment of the LCx, with the optimal result (Figure 4C). In order to determine the cause of acute STEMI,

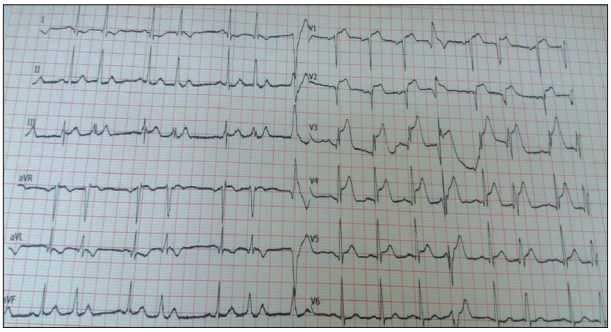

Figure 3. Electrocardiogram shows ST segment elevation V1–V5

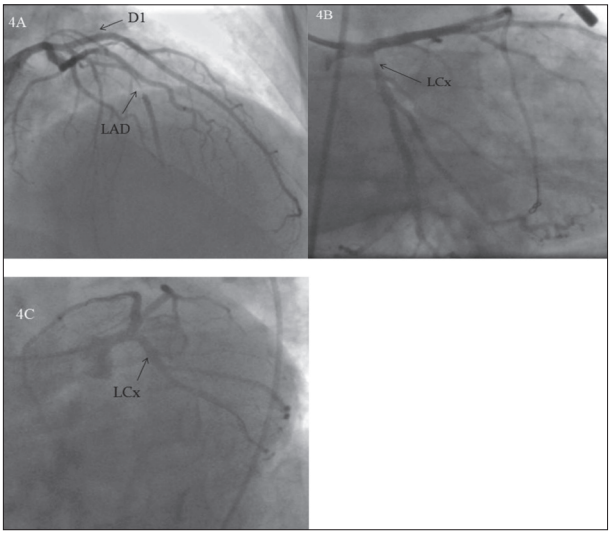

Figure 4. A: Angiography of the left coronary artery showing subocclusive stenosis in the medial segment of the left anterior descending artery (LAD); previously implanted stent in D1 was without thrombosis; B: after implantation of the stents into the left anterior descending artery, significant stenosis of the left circumflex artery was registered; C: the optimal result after percutaneous coronary intervention on the left circumflex artery (LCx)

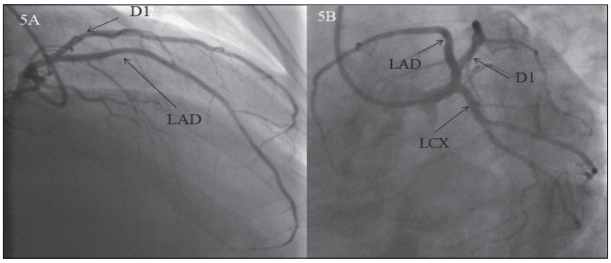

Figure 5. A: After seven days, optimal result in the area of implanted stents in D1 and left anterior descending artery (LAD); B: after seven days, optimal result in the area of implanted stents in D1, the left anterior descending artery, and the left circumflex artery (LCx)

intravascular imaging was performed, seven days after the previous PCI. Optimal result in the area of implanted stents in LAD and LCx were registered on coronarography (Figure 5). Optical coherence tomography (OCT) showed an excellent stent apposition and expansion, but also the duplication in the blood vessel wall in the area below the implanted stents, in proximal LAD and LCx. This duplication represents an unresorbed intramural hematoma as a consequence of SCAD (Figure 6). Since the cause of acute myocardial infarction was SCAD, the patient was switched

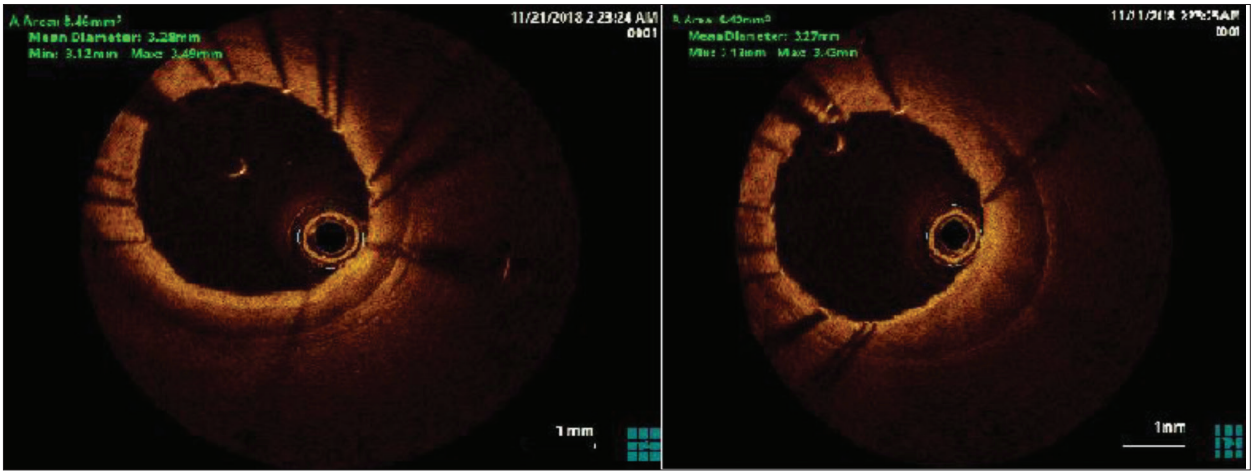

Figure 6. Optical coherence tomography under the stents in the proximal segment of the left anterior descending artery and the left circumflex artery reveals a duplication in the vessel wall; this duplication represents unresorbed intramural hematoma as a consequence of spontaneous coronary artery dissection

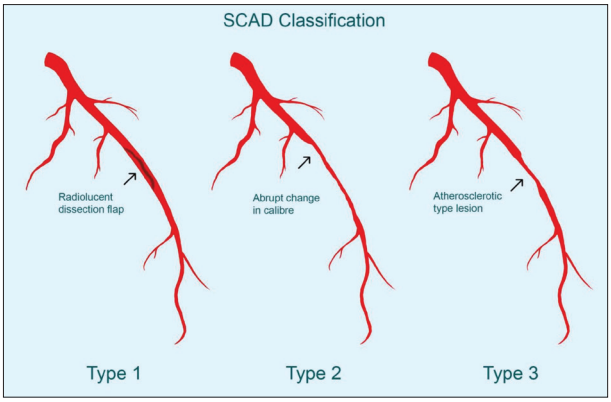

Figure 7. Angiographic spontaneous coronary artery dissection classification system

to clopidogrel, according to recommendations [6]. After six months, exercise stress testing on treadmill (Bruce protocol) was performed. The patient achieved maximal effort (up to 10 METs), without clinical and ECG signs of coronary flow reduction.

Written consent to publish all shown material was obtained from the patient.

DISCUSSION

There are three types of SCAD (Figure 7) [7]. Type 3 is the rarest angiographic manifestation of SCAD, occurring in 3.4% of patients, while the most common is type 2, in about 67.5% of patients [3]. In uncertain cases, intravascular imaging may be helpful. Despite the great importance of intracoronary imaging, caution is needed because of possibility for extension of coronary dissection by using a wire or diagnostic catheter. Seven days after the first coronary event we performed OCT. In the area below the implanted stents in the proximal LAD and LCx, we recognized duplications in the blood vessel wall corresponding to the unresorbed hematoma as a result of SCAD. The lesion in D1 was not recognized as a SCAD type 3. The stent was implanted into the proximal part of D1 and thus prevented the spread of the intramural hematoma further into the diagonal branch. Intramural hematoma propagated in the LAD distal to the first diagonal branch. After the first stent was implanted into the medial part and then the second one into the proximal part of the LAD, intramural hematoma was pushed proximally to the ostium of LCx.

A Spanish multicenter prospective SCAD registry, including 318 patients with SCAD, showed that the artery most frequently involved was the LAD (44%), predominantly affecting the distal segments (39%) and its branches (54%) [8]. In our case, the LAD was also affected by SCAD.

Patients with SCAD were divided into four groups. The first group consisted of patients with hereditary connective tissue disorders associated with arterial wall defect (Marfan syndrome) [9]. The second group represented patients with underlying atherosclerosis, especially men at an average of 55 years [9]. The third group included women in the peripartum period, while the last group consisted of patients with idiopathic SCAD [10, 11]. According to this classification, our patient can be classified into the second group – he is a male, 53 years old, obese, and smoker. It is also important to emphasize that SCAD can be associated with exposure to physical effort, chest trauma, and certain drugs (cocaine, cyclosporine, 5-fluorouracil, and oral contraceptives) [11]. Our patient on the day of the hospital admission was exposed to hard physical effort. Treatment of SCAD includes medical treatment, PCI, and surgical myocardial revascularization. Considering the high risk of complications during PCI, conservative treatment is favored. Also, because of the spontaneous healing of SCAD and the resorption of intramural hematoma in about 70–97% of patients, conservative treatment is advised [12]. A Canadian SCAD cohort study was a multicentric, prospective, observational study of patients with non-atherosclerotic SCAD from 22 centers in North America [13]. The majority of these patients (84.3%), who were being treated conservatively, had good survival rate. However, patients with ongoing ischemia and hemodynamic instability are

to be treated with PCI. In our case, acute STEMI complicated with progredient heart failure indicated primary PCI, which was performed with optimal angiographic results. Data from the literature states that successful PCI is associated with (1) implantation of long stents covering the 5–10 mm proximal and distal edge of the intramural hematoma, (2) direct stent implantation without prior balloon predilatation, (3) balloon dilatation without stent implantation, (4) fenestration of the intramural hematoma by cutting the balloon and decompression of the false lumen, (5) multistent approach by firstly sealing distal and proximal ends with stents, before stenting the middle, and (6) use of bioresorbable stents [14, 15, 16]. Balloon dilation with low-pressure (up to 4 atm) inflations should be used to decrease the risk of perforation [17]. Coronary artery bypass grafting has been described as a treatment strategy for SCAD in patients with left main stenosis and also after technical failure of attempted PCI. According to experts, the basis of medical therapy are acetylsalicylic acid and beta-blockers. Administration of the P2Y12 inhibitors is controversial for patients not treated with PCI. In patients treated with PCI, dual antiplatelet therapy with clopidogrel is recommended [18]. After OCT analysis, which confirmed the SCAD of the LAD, our patient was switched to clopidogrel. Intrahospital survival of these patients is good; however, recurrent spontaneous coronary artery dissections are common. During the follow-up period, our patient was without symptoms of angina. After six months, exercise stress testing on treadmill (Bruce protocol) was performed and the patient achieved maximal effort (up to 10 METs), without clinical and ECG signs of coronary flow reduction. When performing coronarography on younger patients, women in the peripartum and patients with connective tissue disorders, SCAD should be kept on mind, especially if the angiographic finding indicates a possible type 2 or 3 spontaneous dissection. In the future, intravascular imaging could reduce the number of unrecognized and inadequately treated SCAD.

Conflict of interest: None declared.

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Спонтана дисекција коронарне артерије као узрок акутног инфаркта миокарда са *ST* елевацијом

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САЖЕТАК

Увод Спонтана дисекција коронарне артерије (СДКА) дефинисана је као дисекција која није повезана са атеросклерозом, траумом, нити је настала јатрогено.

Приказ болесника Мушкарац старости 53 године је примљен у болницу због болова у грудима и електрокардиографски регистрованих исхемијских промена. Урађена је коронарографија и нађено је 85% сужење прве дијагоналне гране. У истом акту је урађена перкутана коронарна интервенција, са директном имплантацијом леком обложеног стента у прву дијагоналну грану. Око три сата после интервенције код болесника се развио акутни инфаркт миокарда са *ST* елевацијом и урађена је коронарографија. Претходно имплантирани стент у првој дијагоналној грани био је без тромбозе. Нађена је субоклузивна стеноза леве предње силазне артерије те је урађена перкутана коронарна интервенција. После имплантације стента у леву предњу силазну артерију регистовано је сужење на левој циркумфлексној артерији као последица пропагације дисекције. Урађена је перкутана коронарна интервенција и на овој грани. После седам дана, у циљу дефинисања узрока акутног инфаркта миокарда са *ST* елевацијом, урађен је интраваскуларни имиџинг. Оптичка кохерентна томографија показала је одличну апозицију и експанзију стентова. У подручју испод стентова у проксималној левој предњој силазној артерији и левој циркумфлексној артерији региструје се дупликатура у зиду крвног суда. Ова дупликатура представља нересорбовани интрамурални хематом као последицу СДКА.

Закључак Када се изводи коронарографија, код младих људи, жена у перипарталном периоду и болесника са болестима везивног ткива треба мислити на СДКА. Уз интраваскуларни имиџинг, треба настојати да се смањи број непрепознатих СДКА.

Кључне речи: спонтана дискеција коронарне артерије; акутни инфаркт миокарда са *ST* елевацијом; оптичка кохерентна томографија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Liver angiomyolipoma

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SUMMARY

Introduction Benign tumors of the liver are rare. Liver angiomyolipoma is a rare benign mesenchymal tumor that usually occurs in adult female patients. There are four types of hepatic angiomyolipoma: (I) hybrid; (II) myoma type; (III) lipoma type; and (IV) hemangioma type.

Case outline We present a 44-year-old female without symptoms, admitted to the Department of Surgery due to the lesion of the third segment of the liver, measuring 35 × 30 × 15 mm. Tumor was totally excised, and the margins of resection were clean. The differential diagnosis based on radiological findings might be difficult. There are many liver disorders with fatty components, both benign and malignant, e.g., hepatic steatosis, adenoma, lipoma, hepatocellular carcinoma or liposarcoma.

Conclusion Its prognosis is good and the recommended treatment is surgical resection.

Keywords: angiomyolipoma; hepatic tumor; surgery

INTRODUCTION

Benign tumors of the liver are rare with the exception of cavernous hemangioma [1]. Liver angiomyolipoma is a rare benign mesenchymal tumor that usually presents in adult female patients; nonetheless, several cases have also been reported among males [2, 3]. Angiomyolipoma most frequently occur in the kidney, with the liver being the second most common site of involvement [3, 4].

CASE OUTLINE

A 44-year-old symptomless female was admitted to the Department of Surgery in order to have a lesion resection of the third segment of the liver. The patient suffered from posterior mitral valve prolapse with mild regurgitation (no medications) and underwent bilateral knee arthroscopy. Her grandmother has a liver tumor of unknown origin. Ultrasound abdominal examination revealed the liver lesion. Magnetic resonance imaging (MRI) showed the sharply contoured lesion of 30 mm (transverse) × 20 mm (anteroposterior) × 10 mm (craniocaudal), located in dorsal part of the third hepatic segment. The tumor manifested a slight T2 signal hyperintensity and fat-containing component, which quenched in the MRI p-phase. After administration of contrast agent, it was demonstrated that the lesion was heterogenous with enhancing linear partitions inside. In the hepatotropic phase the lesion was not enhanced. The MRI report was ambiguous, and the lesion might be: adenoma, lipoma, hepatocellular carcinoma or angiomyolipoma. The retroperitoneal lymph nodes were within normal limits. The biochemical tests, the tests for hepatic viruses and tumor markers were determined. No active liver disease nor impairment of the synthesizing function of the hepatocytes was revealed. The presence of anti-HBC total was confirmed in repeated tests. However, the other markers of hepatitis B infection were negative. The tumor markers were within normal limits: CA19-9 – 13.73 U/ml and CEA – 0.70 ng/ml. Due to inconclusive additional tests the patient was qualified for laparotomy with surgical resection of the lesion. Intraoperatively the soft tumor of the third hepatic segment measuring 35×30×15 mm was confirmed. Tumor was excised totally, and the margins of resection were clean (R0 resection). The intraoperative ultrasound did not show any other lesions within the liver (Figure 1 and 2). The postoperative course was uneventful. A drain from the subhepatic area was removed on the second postoperative day. The patient has been regularly followed up in the out-patient department.

Gross examination showed solid hepatic tumor. The tumor was gray-yellowish on cut surface. It did not have a capsule but it was well demarcated from liver parenchyma. Histologically, tumor was composed of large, epithelioid smooth muscle cells intermixed with few dispersed mature adipocytes. Smooth muscle cells had epithelioid morphology and abundant, clear to eosinophilic cytoplasm.

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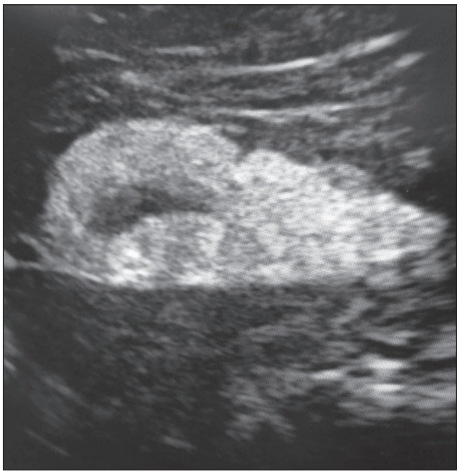

Figure 1. The intraoperative ultrasound view of liver angiomyolipoma

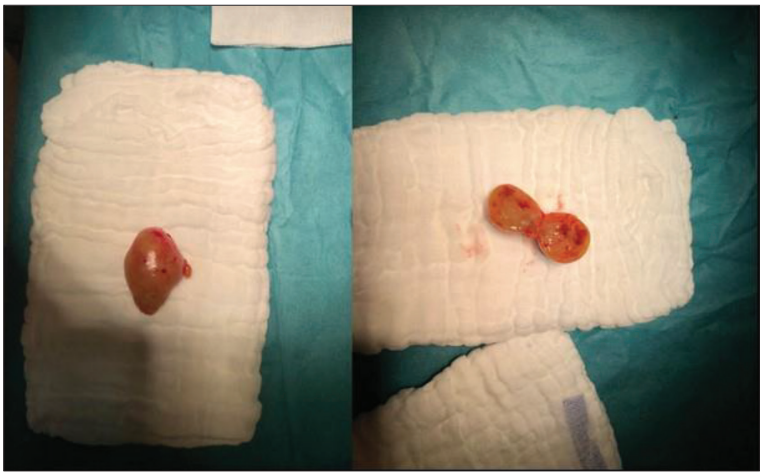

Figure 2. The intraoperative view of the lesion: the ocher tumor measuring 35×30×15 mm

Many blood vessels were also observed, some of them were thick walled. No necrosis, cellular atypia or mitotic figures were noticed. Smooth muscle cells presented characteristic co-expression of muscle markers (smooth muscle actin and focally Desmin) and melanocytic marker HMB45. Histological and immunohistochemical features were consistent with diagnosis of hepatic angiomyolipoma (Figures 3 and 4).

The study was approved by the Commission of Bioethics at Military Medical Chamber in Warsaw (no 173/20), and written informed consent in Polish was obtained from the patient for the publication of this paper.

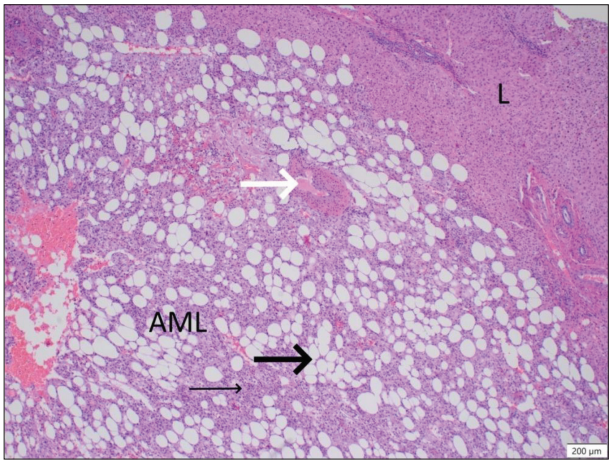

Figure 3. Hepatic angiomyolipoma; the tumor is well demarcated from liver parenchyma (L) and is composed of admixture of epithelioid smooth muscle cells (thin black arrow), mature adipocytes (thick black arrow) and blood vessels (white arrow) (hematoxylin and eosin stain, magnification 400×)

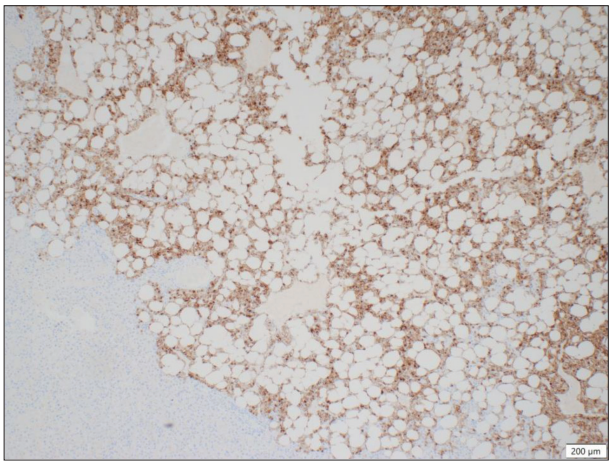

Figure 4. Positive cytoplasmic HMB45 staining of smooth muscle cells (magnification 400×)

DISCUSSION

Primary hepatic angiomyolipoma is a rare tumor. The first case was reported by Ishak [5] in 1976. Hepatic angiomyolipoma can be divided into ten groups based on the tissue components and type of dominant tissue:

(I) hybrid: typical and most common, contains similar proportions of each tissue components within the tumor;
(II) myomatous: smooth muscle cells are the dominant tissue type within the tumor;
(III) lipomatous: adipose tissue is the dominant tissue type;
(IV) angiomatous: vascular tissue is the dominant type;
(V) angiomyomatous;
(VI) myoangiomatous;
(VII) myolipomatous;
(VIII) lipomyomatous;
(IX) lipoangiomatous;
(X) angiolipomatous [6].

The origin of the liver angiomyolipoma is not clearly defined. Angiomyolipoma is associated with tuberous sclerosis in some cases [7]. The differential diagnosis based on radiological findings might be difficult. There are many liver disorders with fatty components, both benign and malignant, e.g., hepatic steatosis, adenoma, lipoma, hepatocellular carcinoma or liposarcoma. Those lesions might

be shown in ultrasound or computed tomography scan, but the MRI is the most sensitive tool [8]. Angiomyolipoma usually occurs as solitary tumor however, some multiple lesions have been described in literature [9]. In the presented case the diagnostics was extended to abdominal MRI with contrast, which allow to qualify whether the patient is for surgery. In MRI with contrast, angiomyolipoma tumors might be enhanced depending on the ratio of their fatty to vascular components. The complete lack of contrast enhancement may suggest liver lipoma [9].

Despite the fact that it is a benign neoplasm, malignant features such as infiltration of surrounding tissues, relapse after resection or distant metastases have sometimes been observed. The main predictor of malignancy is not so much the tumor size as its growth rate and the presence of atypical cells [10]. This rare, but non-negligible, potential for malignancy makes hepatic angiomyolipoma an even greater clinical problem. It is considered, that surgical management is suggested to patients with the following criteria: tumor size greater than 5 cm, with clinical symptoms, faster tumor growth, the tumor located at the first, fourth, fifth or eighth segment of the liver [11]. In case of a decision on conservative treatment, it is necessary to regularly monitor patients in order to observe the dynamics of the growth of the lesion and early detection of symptoms. However, sometimes large tumors may rupture and bleed. This causes the patient to develop acute abdominal symptoms and urgent surgery is required [12].

In conclusion, liver angiomyolipoma is a rare benign tumor, usually asymptomatic, and detected during routine radiological tests. The differential diagnosis with other hepatic tumors by means of radiological tests is very difficult and sometimes impossible. Its prognosis is good and the recommended treatment is surgical resection.

Conflict of interest: None declared.

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Ангиомиолипом јетре

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САЖЕТАК

Увод Бенигни тумори јетре су ретки. Ангиомиолипом јетре је редак бенигни мезенхимски тумор који се обично јавља код одраслих болесника. Постоје четири врсте ангиомиолипома јетре: (I) хибридни; (II) тип миома; (III) тип липома и (IV) тип хемангиома.

Приказ болесника Представљамо жену од 44 године, без симптома, која је примљена на одељење хирургије због лезије трећег сегмента јетре, димензија 35 × 30 × 15 милиметара. Тумор је у потпуности уклоњен, а маргине ресекције су биле чисте. Диференцијална дијагноза заснована на радиолошким налазима може бити тешка. Постоје многи поремећаји јетре са масним компонентама, и бенигни и малигни, нпр. хепатичка стеатоза, аденом, липома, хепатоцелуларни карцином или липосарком.

Закључак Прогноза је добра, а препоручени третман је хируршка ресекција.

Кључне речи: ангиомиолипома; тумор јетре; хирургија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Fistula of a pancreatic pseudocyst into the superior mesenteric and portal veins causing erythema nodosum and aseptic polyarthritis – case report and review of literature

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SUMMARY

Introduction Extra-pancreatic complications of acute and chronic pancreatitis that do not relate to vital organs are rare. The most common include subcutaneous paniculitis, arthritis, bone marrow fat necrosis, and vasculitis. These associated conditions have been termed pancreatic disease syndrome (PDS), which can occur not only with pancreatitis but also in other pancreatic diseases. PDS is believed to be caused by circulating pancreatic enzymes, which can occur when the pancreas is in direct communication with the circulation. Pancreatic pseudocyst erosion into the superior mesenteric and portal veins is extremely rare; and there have only been 22 previously reported cases in literature. The authors endeavoured to describe a manifestation of PDS with formation of a pseudocystic-portal fistula, its complications, and propose adequate surgical management.

Case outline We present a 37-year-old man with chronic alcoholic pancreatitis and a pancreatic pseudocyst within the head of the pancreas which communicated with the main pancreatic duct on one side and eroded into the superior mesenteric and portal veins on the other, causing erythema nodosum-like vasculitis, and polyarthritis. The patient was initially treated conservatively, but subsequently required multiple arthrotomies and finally underwent pylorus preserving duodenopancreatectomy and direct repair of the affected veins.

Conclusion The majority of cases required aggressive surgical intervention due to heightened risk of hemorrhage. In patients who develop disseminated fat necrosis, an earlier surgical intervention can be justified. The authors would recommend that, where practical, a pylorus-preserving pancreaticoduodenectomy should be performed.

Keywords: pancreas; pseudocyst-portal vein fistula; pancreatic disease syndrome

INTRODUCTION

Pancreatic pseudocysts often follow acute pancreatitis, and though they can resolve spontaneously, they can also be associated with potential complications. These include bleeding [1, 2], ruptures into the abdominal cavity [3], splenic vein obstruction [4], portal vein thrombosis [5, 6], and the formation of fistulae into the surrounding organs [6, 7, 8] and the inferior vena cava [9]. Erosion of a pancreatic pseudocyst into the portal vein to create a pancreas duct – portal vein fistula (PPF), however, is extremely rare, with only 22 other previously reported cases [5, 6, 10–28].

CASE REPORT

A 37-year-old man, with a 15-year history of alcoholism, presented with worsening epigastric pain requiring admission to a peripheral hospital. On examination he was found to have a tender upper abdomen and had a hematest-positive melaena stool. Apart from a moderate leucocytosis, other laboratory tests were within normal limits. An upper endoscopy revealed a hiatus hernia and *Helicobacter pylori* gastropathy. An ultrasound (US) scan defined a 5 × 4.5 cm hypoechogenic lesion within the uncinate process of the pancreas, which on computed tomography (CT) scan appeared to be inhomogeneous with a 2 cm central hypodense area. A US-guided fine needle aspiration of the lesion produced a dark green-rusty dense fluid, with a high pancreatic enzyme content. Though anti-*Helicobacter pylori* treatment gave only mild relief of his symptoms, he refused operative drainage of the pancreatic pseudocyst, taking his own hospital discharge.

Two weeks later he was admitted to a second hospital with worsening abdominal pain, and four days later developed erythema nodosum-like cutaneous lesions on the front and sides of both his lower legs. Within two weeks, he had developed a moderate fever, raised serum and urine amylase, generalized arthralgia, restricted

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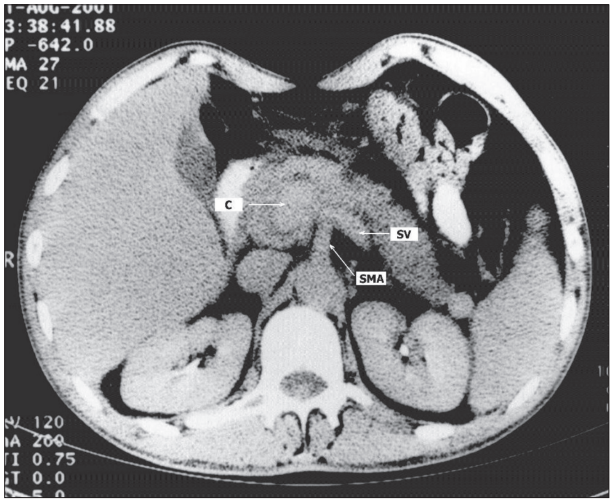

Figure 1. Computed tomography showing contrast within the central area of the cyst – C;
SV – splenic vein; SMA – superior mesenteric artery

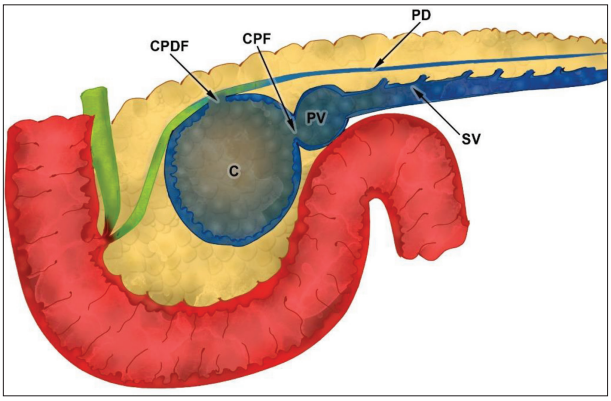

Figure 2. Diagram showing operative findings;
C – pancreatic pseudocyst; PV – portal vein; SV – splenic vein; PD – pancreatic duct; CPF – cyst portal fistula; CPDF – cyst pancreatic duct fistula

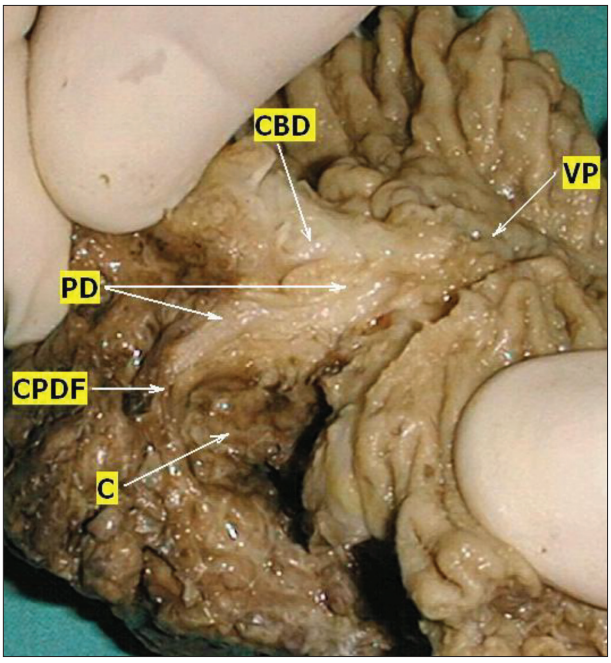

Figure 3. The intra-operative specimen;
C – pancreatic pseudocyst; PD – pancreatic duct; CPDF – cyst pancreatic duct fistula; VP – Vater's papilla; CBD – common bile duct

active and passive joint motion, and swelling of all the major joints.

He was transferred to our institution because of a clinical deterioration, and on admission was found to be pale and lethargic, with generalized arthralgia, large joint effusions, and abdominal pain. His fibrinogen was 10.4 g/L, white blood cell count 25×10^9/L, and erythrocyte sedimentation rate 110/1h. The cyst within the head of the pancreas had recollected on repeat CT, and now demonstrated a central contrast-enhancing area (Figure 1). He passed further melaena stool after admission, but a repeat upper endoscopy once more showed no active bleeding site.

Over the next 24 hours, he developed spontaneous discharge of a dense, viscous, light-brown pus-like material from his swollen left knee. Surgical arthrotomies of his other large joints were performed, after which his joint pains and swellings resolved. Neither direct examination nor cultures of the joint samples were positive for bacteria, and histology found only non-specific aseptic inflammation of the synovial membranes and joint capsules.

Despite a general improvement in his condition, the patient's epigastric pain continued and the decision was made to operate on the pancreatic pseudocyst. At laparotomy, a cyst-like lesion was found within the head of the chronically inflamed pancreas, close to the mesenteric vein. No fat necrosis was found within the abdomen. Cyst aspiration was performed and blood-like aspirate obtained; containing 58,040 U/L of amylase on laboratory analysis. The cyst was formally opened with the aim of performing a cystojejunostomy, particularly as there was a chance that the blood that had been aspirated might have been from an accidentally punctured blood vessel. Following exploration, the bleeding became more brisk, requiring tamponade, and fearing an arterial aneurysm, a pylorus preserving pancreatic head resection was performed.

After pancreatic transection, the head was slowly and carefully dissected from the very adherent superior mesenteric and portal veins. Unfortunately, the brisk bleeding continued, and the bleeding source was established as a 2.5×0.5 cm communication between the cyst cavity and the portal vein (Figure 2). A temporary clamp was placed to control the bleeding and the fistula was oversewn, making use of the thickened cyst wall.

Pathological analysis of the resected specimen confirmed a broad fistula between the cyst (and the superior mesenteric) and portal veins; an additional fistula was also identified between the cyst and the pancreatic duct (Figure 3).

The patient's postoperative recovery was uneventful, with an almost immediate resolution in his abdominal symptoms. After a rehabilitation programme and intense physiotherapy, the patient regained most of his musculoskeletal function, remaining ambulatory and well at a recent six-year review.

This case report was approved by the institutional ethics committee, and written consent was obtained from the

patient for the publication of this case report and any accompanying images.

DISCUSSION

The precise mechanism of PPF formation remains unknown [10]. Pancreatic enzymes activated by intestinal enterokinases are thought to be responsible for the erosion into the neighbouring blood vessels [14]. Any venous thrombosis in these vessels is then likely to be dissolved by these same enzymes, thereby allowing their free flow into the blood circulation, causing PDS [18].

There have been 22 previously documented cases of PPF, almost all being single-case reports [5, 6, 10–28]. Including this currently reported case, these have been predominantly male patients (82% or 19/23 patients), with a mean age of 50 years (range 29–82 years) at presentation and most had a history of chronic alcohol abuse and chronic pancreatitis. The majority presented with abdominal pain and of those tested all had a raised serum amylase [22]. One patient had recurrent gastrointestinal bleeding and pain [18].

Fifteen (65%) had pseudocyst formation in the head of the pancreas (in close proximity to the portal vein), and four patients had pseudocysts involving the tail. Including the current case, 10 (43%) were suffering from PDS [14, 17, 22], erythema nodosum was evident in eight (35%) [10–16, 22], polyarthritis in seven (39%) [11–17], and disseminated fat necrosis in five (28%) patients [17, 22].

Conventional invasive and noninvasive imaging can often (though not always consistently) identify a PPF [22]. Contrast-enhanced CT scan can demonstrate a thrombus within the portal vein in PPF patients, though does not typically demonstrate the fistula. Magnetic resonance and magnetic resonance cholangiopancreatography (MRI/MRCP) can demonstrate an increased fluid signal in the portal vein, assess the pancreatic ductal system, and identify other extrinsic pathology. US can also demonstrate absent portal vein flow from thrombus formation, but not necessarily the fistula formation. Endoscopic retrograde cholangiopancreatography (ERCP) will demonstrate a fistula but only if the pseudocyst directly connects to the pancreatic duct. Percutaneous transhepatic portography (PTP) by definition directly visualizes the portal system and can also yield portal vein fluid for analysis [22]. Image-guided (CT or US) cystography and angiography can also be useful.

Of the (now 23) reported PPF cases, four (17%) were diagnosed through ERCP [5, 6, 23, 24], four (17%) through cystography [19, 20, 27], three (13%) through PTP [18, 21, 22], two (11%) through MRI/MRCP [25, 26], one through CT [28], and one (4%) through angiography [11].

In this particular reported case, despite having had two upper endoscopies, an US, and two CT scans, the diagnosis of a PPF was only actually made during surgery and then confirmed through histopathological analyses. Of the remaining reported PPF cases, two were similarly diagnosed during surgery [12, 17], while five (22%) were only discovered at post mortem [10, 13–16]. Thus, despite multimodal diagnostics, eight (35%) patients had their diagnosis established either at surgery or at post mortem.

The majority of these patients can be managed expectantly, and PPF have been known to close spontaneously [23]. However, prompt surgical intervention is indicated where dessminated fat necrosis develops or when there is a significant clinical deterioration, as these are associated with significantly poorer outcomes, and even death [6, 15, 25].

Nine of the 23 PPF patients underwent surgery. A pylorus preserving pancreaticoduodenectomy was performed in two patients [12, 22], similar to the procedure which our patient also underwent, resulting in the immediate resolution of the PDS. Another patient underwent surgical ligation of the incoming vessels with no symptom improvement. A Whipple's procedure was then performed at a second sitting, which resulted in the disappearance of the "PDS" [11]. A fifth patient underwent local pancreatic resection and panceaticojejunostomy; unfortunately, this patient had a recurrence of subcutaneous fat necrosis, but fortunately responded to steroids [17]. An unusual sixth patient with three cysts underwent splenectomy and a partial left pancreatectomy. Following this, the dilated pancreatic duct and the pancreatic pseudocyst walls were opened longitudinally and a "Y" side-to-side pancreaticojejunostomy was performed. A catheter was then inserted through the splenic vein into the portal tree to drain it externally and to prevent portal hypertension during the postoperative period. The catheter stopped draining pancreatic juice after a few days and the drain was removed 15 days postoperatively [20]. This patient was doing well at the time of publication two years after surgery. A seventh patient had simple operative drainage of their ascites and after three months was discharged from hospital. They were noted to be well at the time of publication [19]. However, no time period for this was stated. One further patient underwent pancreaticojejunostomy [18], another a pancreaticoenterostomy [25].

Despite the successful closure of the PPF, some of these surgically managed patients continued to suffer serious disability from ongoing recurrent extrapancreatic disease.

Our patient clearly suffered from chronic alcoholic pancreatitis with an associated pseudocyst. However, we failed to recognize that the pre-operative dark brown aspirated fluid and the presence of contrast within the central area of the cyst on CT indicated a probable communication of the cyst with a neighbouring blood vessel. In retrospect, these findings obviously warranted angiographic imaging. The absence of contrast within the peripheral area of the cyst should also have been recognized as resulting from thrombosis. The laboratory findings of high concentrations of amylase from the intraoperative blood aspirated from the cyst would have also indicated a possible cyst–portal fistula. The upper gastrointestinal bleeding with a normal upper endoscopy can also be explained by the pathology finding of a communication between the pancreatic pseudocyst and the pancreatic duct; and this could have been identified earlier by ERCP. The direct emptying of the

pancreatic enzymes into the mesenteric and portal veins was probably the cause of PDS, which completely resolved after surgery.

The authors would recommend that, where practical, a pylorus-preserving pancreaticoduodenectomy should be performed. This resulted in a rapid resolution in our patient's PDS symptoms, which has also been the experience of other authors with similar cases [12, 22].

Conflict of intrest: None declared.

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Фистула панкреасне псеудоцисте са горњом мезентеричном и портном веном која је довела до нодозног еритема и асептичног полиартритиса – приказ болесника и преглед литературе

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САЖЕТАК

Увод Екстрапанкреатичне компликације акутног и хроничног панкреатитиса које се не односе на виталне органе су веома ретке. Најчешће компликације су супкутани паникулитис, артритис, масна некроза косне сржи и васкулитис. Ова асоцирана стања се једним именом називају синдром болести панкреаса и могу се јавити не само уз панреатитис већ и у другим болестима панкреаса као што су тумори, траума и литијаза панкреатичних канала. Синдром болести панкреаса је вероватно узрокован циркулишућим ензимима панкреаса (конкретно липазе) када је панкреас у директној комуникацији са крвотоком. Ерозија псеудоцисте панкреаса у горњу мезентеричну и портну вену је веома редак догађај; постоје само 22 претходно објављења случаја панкреатично-порталних венских фистула у литератури. Аутори су настојали представити обољење које настаје код синдрома болести панкреаса ретким формирањем псеудоцистично-порталне фистуле, могуће компликације, уз препоруку о адекватном хируршком третману са детаљним прегледом светске литературе.

Приказ болесника Представљамо необичан случај тридесетседмогодишњег човека са хроничним алкохолним панкреатитисом и псеудоцистом главе панкреаса која једном страном комуницира са главним панкреатичним водом, а другом је широком ерозијом у контакту са горњом мезентеричном и портном веном, изазивајући васкулитис налик нодозном еритему (*Erythema nodosum*) и полиартритис. Иницијално, болесник је лечен конзервативно, али су накнадно урађене многоструке артротомије када је у крајњем акту урађена пилорус-презервирајућа дуоденопанкреатектомија и директна реконструкција оштећених вена.

Закључак Већина случајева захтевала је агресивно хируршко лечење, јер је опасност од крварења велика. Ранија хируршка интервенција може бити оправдана и ако се код болесника развија дисеминована некроза масти која додатно погоршава исход. Аутори препоручују да се у пракси учини пилорус-презервирајућа панкреатикодуоденектомија.

Кључне речи: панкреас; псеудоцистично-портална венска фистула; синдром болести панкреаса

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Super-refractory status epilepticus and pharmacoresistant epilepsy in an infant with hemorrhagic shock and encephalopathy syndrome

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SUMMARY

Introduction Hemorrhagic shock and encephalopathy syndrome (HSES) is a rare disorder with prevalence at an early age. The main features of HSES are acute diarrhea, shock, disseminated intravascular coagulation, multisystem impairment, and encephalopathy. The prognosis is very poor, with high mortality, especially in cases with status epilepticus.

Case outline The presented infant had typical features of HSES associated with super-refractory status epilepticus as *de novo* epileptic event, followed by pharmacoresistant epilepsy. Clinical course of the disease was very severe and required urgent circulatory and respiratory support, and simultaneous management of super-refractory status epilepticus by continuous intravenous infusion of midazolam, barbiturate, and levetiracetam. The outcome was very poor with serious neurological consequence and resistant epileptic seizures.

Conclusion The treatment of the presented patient with HSES was very challenging due to a life-threatening condition associated with super-refractory status epilepticus, and further pharmacoresistant epilepsy. Additionally, the choice of antiepileptic drugs is limited due to multisystem impairment and adverse effects which might worsen the already severe course of the disease.

Keywords: status epilepticus; hemorrhagic shock and encephalopathy syndrome; pharmacoresistant epilepsy

INTRODUCTION

Hemorrhagic shock and encephalopathy syndrome (HSES) was described by Levin et al. [1] as a new syndrome in 1983. Few series or case reports of patients with HSES have been presented over the last 30 years. The authors described a very severe clinical course of the disease, with poor prognosis [2]. Nine criteria for HSES have been defined: shock; coma and/or seizures; diarrhea; disseminated intravascular coagulation; fall of hemoglobin and platelet count; elevated liver enzymes; renal dysfunction; acidosis; negative blood and cerebrospinal fluid cultures. Diagnosis of HSES is definitive if all nine criteria are satisfied, while probable HSES is if either eight criteria are satisfied, or at least seven with no information on the remainder. The initial manifestation of the disease is acute diarrhea with very rapid development of circulatory shock, encephalopathy associated with epileptic seizures, disseminated intravascular coagulopathy with multisystem impairment including liver and kidneys [1, 2, 3]. Status epilepticus (SE) in children with HSES frequently emerged in preceding etiologies with augmented neuronal excitability by distinct pathomechanism from the "cytokine storm"–mediated acute seizures during childhood [4]. Super-refractory status epilepticus (SRSE) is defined if SE continued or recurred 24 hours or more after the onset of anesthetic drugs in continuous infusion, and is associated with morbidity and mortality [5]. The main neuroradiological feature during the first phase of the disease is cerebral edema, followed by brain atrophy [6]. Treatment of HSES is very urgent and includes intensive care therapy with multidisciplinary approach. Despite prompt and adequate treatment, morbidity and mortality are still very high [2, 3].

The literature data about characteristics of epileptic seizures in infants with HSES are insufficient, and there is no data about the association with SRSE.

The aim of our case presentation is to point out the challenge in diagnosis and treatment in infant with HSES, particularly if it is associated with SRSE and epileptic seizures

CASE REPORT

We present an infant aged three months with a severe course of HSES, SRSE, and resistant epilepsy. Somnolence with progression to coma started in the morning of the admission day, with signs of cyanosis and periods of apnea, together with jerking of the right side of the body for hours, followed by secondary generalization of the seizure. The data about previous history were insufficient, but we found out

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Table 1. Initial laboratory findings

Analyses	Results	Comment according to referent value
White blood cell count Hemoglobin (g/L) Platelets	10.4 117 86	Normal Decreased Decreased
C-reactive protein (mg/l)	0.9	Normal
Blood pH	7.27	Decreased
Base excess	-10.7	Increased
Bicarbonate (mmol/l)	13	Decreased
Glycaemia (mmol/l)	1.6	Decreased
Urea (mmol/l)	13.7	Increased
Sodium (mmol/l)	133	Decreased
Potassium (mmol/l)	1.6	Decreased
Calcium total (mmol/l)	1.83	Decreased
Lactate dehydrogenase (U/l)	4622	Increased
Creatine phosphokinase (µg/l)	5705	Increased
Bilirubin total (mg/dl)	12.2	Decreased
Ammonium (µmol/L)	44	Normal
Uric acid (µmol/L)	1156	Increased
Albumin (g/l)	29	Decreased
Liver enzymes AST (IU/l) ALT (IU/l)	 603 343	 Increased Increased
Prothrombin time (s) (%)	47.4 (13)	Prolonged
Partial prothrombin time (s)	53.8	Prolonged
D-dimmers	5100	Increased

AST – aspartate aminotransferase; ALT – alanine transaminase

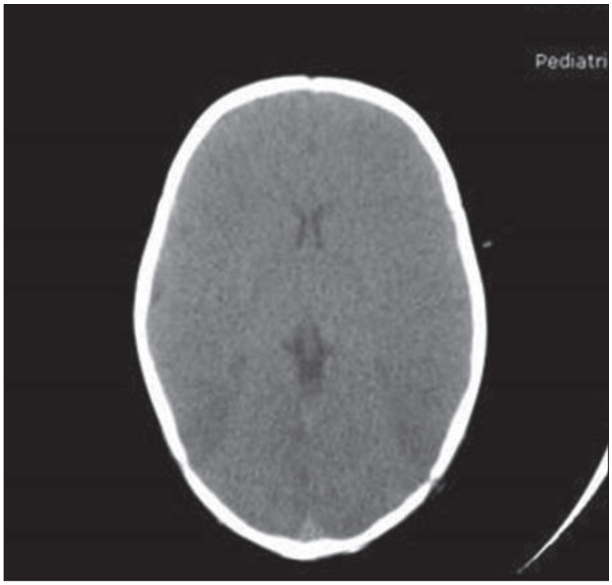

Figure 1. Brain computerized tomography scan at the level of the lateral ventricles showing a severe cerebral edema with obliteration of the lateral ventricles, loss of differentiation of the gray/white matter, and cortical sulci and gyri

that the infant was the third child in the family, from an uneventful pregnancy and delivery.

The infant was admitted to the pediatric intensive care unit of our institute due to coma and generalized SE with irregular respiration. The patient was febrile, pale with perioral cyanosis, extremely dehydrated, with signs of circulatory shock associated with numerous watery diarrheas. Hart rate was increased, 180–200 beats/minute for the first three days, while blood pressure was decreased. Oliguria to anuria lasted two days despite hydration, circulatory support, and diuretics. During the first five days in the hospital, the infant suffered severe watery and bloody diarrhea, with more than 15 stools per day. The results of biochemical and hematology analyses are presented in Table 1. Focal onset seizures with secondary generalization repeated frequently for seven days despite anticonvulsive treatment and hemodynamic stabilization. The signs of right hemiparesis were noted after seven days when the child became more active with spontaneous movements. Imaging chest X-ray and abdomen ultrasound were normal. Microbiological and serological analyses of the blood, urine, stool, and cerebrospinal fluid were negative for bacteria and viruses (herpes simplex virus, enterovirus, adenovirus, and rotavirus). Initial computerized tomography (CT) showed a significant brain edema (Figure 1), especially above the posterior regions, which was the cause of postponing the lumbar puncture.

Initial treatment included intensive care measures of circulatory and respiratory support, rehydration, correction of acidosis and electrolyte disturbances, diuretic stimulation and antibiotics, antiedematous therapy (mannitol, dexamethasone) started after brain edema CT scan evidence and was administered for seven days. During the first few days, the function of circulatory and respiratory systems, the kidney, and the liver was improved. Despite circulatory and respiratory stabilization, the condition of the infant was very critical due to coma and frequent and prolonged epileptic seizures, mostly with jerking of the right side of the body, with spreading to the left side and generalization. The seizures were resistant to the high dosage of intravenous bolus of benzodiazepines (midazolam 0.2 mg/kg), phenobarbital (20 mg/kg), and levetiracetam (60 mg/kg). Since the failure of the first and second antiseizure drugs, anesthesia with continuous intravenous infusion of midazolam was started and the dosage was increased up to 0.4 mg/kg/h. Every withdrawal of anesthesia was associated with recurring seizures, and continuous infusion of midazolam lasted eight days. After the cessation of generalized tonic–clonic SRSE, and midazolam withdrawal, the infant continued to suffer frequent focal onset seizures with aversive head-turning, and jerking of the right side of the body, with secondary generalization. Valproate was started as soon as the liver enzymes were normalized. Since the infant suffered episodes of irritability, agitation, and long-lasting monotone crying, clonazepam was added to valproate. Serial video electroencephalography (EEG) showed very slow and low amplitude background activity with multifocal epileptic discharges. The focal seizures were resistant to the combination of valproate and clonazepam, so carbamazepine was introduced. After seven days, when the dosage was increased up to 15 mg/kg, the infant started having terrible myoclonic jerks. Ictal video EEG showed multiple spikes and poly-spikes and waves synchronized with myoclonic jerks. Since carbamazepine might provoke myoclonic jerks, the drug was stopped and topiramate was introduced. With increasing the dosage of topiramate up to 5 mg/kg/day, the frequency

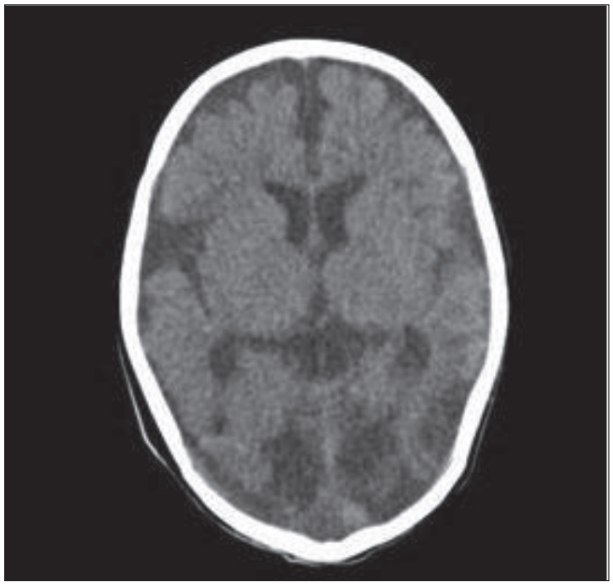

Figure 2. Brain computerized tomography scan at the level of the lateral ventricles showing structural changes: encephalomalacia, brain atrophy, hydrocephalus ex vacuo with sparing of the basal ganglia, cerebellum, and brain stem

of seizures decreased and further good control of seizures was achieved. We noticed improvement in seizure control, but not in neurological status. After 70 days of hospitalization, the infant was discharged and referred to a regional hospital with very severe neurological consequences presented as: cortical blindness, right spastic hemiparesis, increased muscle tone of extremities with bilateral positive Babinski sign and feet clonus, the only voice was in the form of monotonic crying, the feeding was through nasogastric tube because of loss of sucking and swelling reflex. CT scan during hospitalization showed progressive brain atrophy (Figure 2). During two years follow-up period, the child was seizure free, while neurological consequences were severe including blindness, microcephaly, and right-sided hemiparesis, unable to sit, stand and walk.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written consent to publish all shown material was obtained from the patient's caregiver.

DISCUSSION

HSES is a very severe complication of gastroenteritis with high mortality of 60%, and with severe neurological consequences in survived patients [2]. Predictors for poor prognosis are SE, prolonged coma, and biphasic course of the disease [2]. Our patient had two of the three predictors for poor outcome – SE and prolonged coma. Neuroradiological finding was typical for HSES in our case, showing severe brain edema at the onset, and later progressive brain atrophy. Literature data also suggest a correlation between the severity of neuroradiological brain abnormalities and poor outcome, as was in our case [2, 6, 7]. Pathogeneses of the neurological manifestations of HSES is still unknown, so there are several hypotheses. According to some of them, ischemia and hypoxia have the main roles due to circulatory impairment, while hyperthermia is less probable. Direct bacterial or viral neurotoxicity is also possible in pathogenesis of HSES [8, 9]. A very recent study supports "cytokine storm" pathogenesis of HSES, showing significant increases in levels of most inflammatory cytokines and all chemokines in six patients with HSES but no significant difference in levels of some cytokines (IL-2, IL-4) within 24 hours of symptom onset [10]. Similar to other reported studies, there is no effect on mortality when immunomodulatory treatments, such as corticosteroids, are used [10, 11].

The treatment of seizures including SE is a very challenging part of therapeutic approach in HSES. Literature data presented that SRSE was associated with resistance on antiseizure medication and high case–fatality rate (21.3%) [12, 13]. In a new-onset seizure presenting as *de novo* refractory SE, it is very important to explore the underlying etiology, especially the central nervous system inflammation, as well as to start appropriate etiological treatment early [13]. We showed that continuous infusion of midazolam in high dosage with careful monitoring of the vital signs could be a good choice for treatment of SRSE in patients with the HSES. The subsequent episodes of excitability and crying in our case might have been caused by midazolam withdrawal and/or were the manifestation of the disease. Nevertheless, the treatment by clonazepam was effective in those episodes. There is no data on patients with HSES having myoclonic jerks spontaneously, but we observed myoclonus in our patient provoked by carbamazepine. Topiramate in combination with clonazepam was very successful in our patient for the long-term seizure control and irritability. Prognosis in most children with HSES is poor and associated with high mortality and morbidity rate, although a recent publication on HSES in several adult patients suggested a favorable outcome [14, 15].

In conclusion, encephalopathy and epileptic disorders might exist during and after the recovery of multisystem impairment in patients with HSES. In our patient, SRSE and epileptic seizures were dominant and long-lasting features of the disease. Some antiepileptic drugs are limited due to multisystem impairment and adverse effects which might worsen already severe course of the disease. SE in HSES has a predictive value, and despite adequate treatment, SRSE contributed to poor prognosis in our case. Multicenter studies are recommended to achieve better understanding of pathogenesis including epileptogenesis, and treatment of this rare disorder.

Conflict of interest: None declared.

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Суперрефрактарни епилептички статус и фармакорезистентна епилепсија код одојчета са синдромом хеморагијског шока и енцефалопатије

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САЖЕТАК

Увод Синдром хеморагијског шока и енцефалопатије редак је поремећај који има преваленцију у раном узрасту. Главна обележја овог синдрома су акутни пролив, дисеминована интраваскуларна коагулација, мултисистемско оштећење и енцефалопатија. Прогноза болести је лоша и удружена је са високим морталитетом, нарочито ако је ток компликован епилептичким статусом.

Приказ болесника Приказано је одојче са типичним карактеристикама синдрома хеморагијског шока и енцефалопатије удруженим са суперрефракторним епилептичким статусом као новим епилептичким догађајем, који је праћен фармакорезистентном епилепсијом. Клинички ток болести је био веома тежак, а одојче је захтевало хитну респираторну и циркулаторну потпору, а у исто време збрињавање суперрефрактарног епилептичког статуса применом континуиране инфузије мидазолама, барбитурата и леветирацетама. Исход болести је неповољан, са тешким неуролошким секвелама и фармакорезистентном епилепсијом.

Закључак Лечење приказаног болесника са синдромом хеморагијског шока и енцефалопатије је велики изазов због животно угрожавајућег стања које је удружено са суперрефрактарним епилептичким статусом и резистентном епилепсијом у каснијем току болести. Отежавајућа околност је ограничен избор антиепилептичких лекова због мултисистемског оштећења и нежељених ефеката, који додатно могу погоршати ионако тежак ток болести.

Кључне речи: *status epilepticus*; синдром хеморагијског шока и енцефалопатије; фармакорезистентна епилепсија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Video-assisted thoracoscopic surgery for primary hyperparathyroidism with ectopic parathyroid adenoma in thymus

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SUMMARY

Introduction Primary hyperparathyroidism is rare pathology in children (2–5:100,000). In more than 85% of patients, a single adenoma is present, and its extirpation is usually the only treatment a patient requires. In approximately 15–80% of cases, ectopic mediastinal parathyroid tissue can be found inside the thymus.

Case outline Our patient was a 13-year-old boy, who presented with multiple bone fractures in the previous period of time, and fatigue. Parathyroid hormone levels preoperatively were extremely high (1320 pg/ml – more than 19 times higher than normal). Serum calcium was also elevated (total 3.55 mmol/l; ionized 1.41 mmol/l). He was examined and diagnosed as primary hyperparathyroidism by a pediatric endocrinologist. Imaging procedures for the preoperative localization of parathyroid adenomas were done (^{99m}Tc sestamibi scintigraphy and magnetic resonance imaging suggested ectopic mediastinal parathyroid adenoma). The patient underwent video-assisted thoracoscopic surgery procedure. After exploration of the mediastinum and chest, no ectopic parathyroid tissue was found, so total thoracoscopic thymectomy was performed. Final pathological section confirmed parathyroid adenoma inside the thymus.

Conclusion We believe that if no parathyroid tissue is found during surgical exploration of mediastinum, in a child with preoperatively detected parathyroid adenoma in anterior mediastinum, recommendation is to think about possible intrathymic localization and consider removing the thymus. Greater sample size is necessary for higher reliability of this statement.

Keywords: primary hyperparathyroidism; video-assisted thoracoscopy; thymectomy; Tc-99msestamibi parathyroid scan; children

INTRODUCTION

Primary hyperparathyroidism (PHPT) is rare in pediatric patients (2–5:100,000) and only about 200 cases have been reported [1]. Clinical presentation can include unspecific symptoms of gastrointestinal, musculoskeletal, renal, and neurological systems, but also very specific such as pathological bone fractures, kidney stones, or pancreatitis [2]. It is usually diagnosed by an endocrinologist, however appropriate treatment for insufficiently controlled PHPT is mainly surgical. PHPT is principally caused either by adenoma or hyperplasia of parathyroid glands. In more than 80% of patients, a single adenoma is present, and its extirpation is usually the only treatment a patient needs [3, 4, 5]. Preoperatively, it is necessary to detect hypersecreting gland(s) or to locate adenoma. This can be achieved using ultrasound, magnetic resonance imaging (MRI), computerized tomography (CT) or radioisotope scan. Also, intraoperative monitoring of parathyroid hormone (PTH) levels, frozen section biopsy, handheld gamma probe or methylene blue infusions should be used as a direct control of the adequate extirpation [6]. The goal of the surgical treatment is to identify and remove all abnormal parathyroid tissue.

The purpose of the study was to present our first experience in such a rare pathology, and to consider treatment options when pre- and/or intra-operative mass detection is inconclusive.

CASE REPORT

Our patient was a 13-year-old boy, who presented with multiple bone fractures in the previous period and fatigue. He was examined and diagnosed as PHPT by a pediatric endocrinologist. PTH levels were extremely high (1320 pg/ml – more than 19 times higher than normal). Serum calcium was also elevated (total 3.55 mmol/l; ionized 1.41 mmol/l), serum phosphorus was low (0.45 mg/dl), alkaline phosphatase was normal, 25-hydroxyvitamin D (25OHD) was low (29 nmol/l) and biochemical markers of bone turnover were also high (CrossLaps 2895 pg/ml

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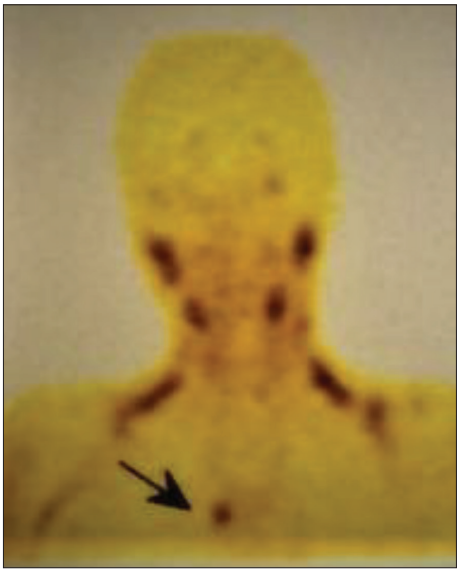

Figure 1. Preoperative diagnostics – 99mTc-sestamibi scan showed intensive focal uptake in mediastinum

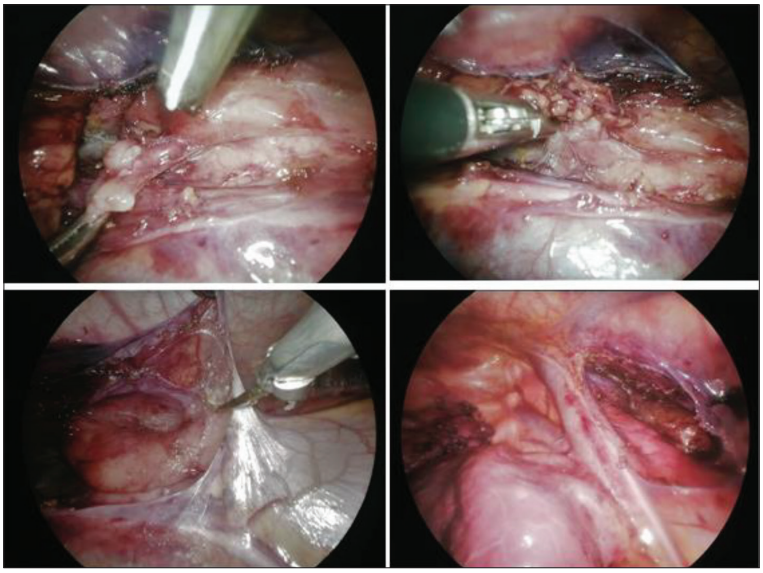

Figure 2. Intraoperative details – suspicious mass (without parathyroid tissue) extirpation (upper row) as well as initial and final step of thoracoscopic thymectomy (lower row)

and P1NP > 1200 ng/ml). Urinary excretion of calcium was high with urinary calcium/creatinine ratio of 2.1. We did biochemical screening for hyperparathyroidism and the other multiple endocrine neoplasia type 1 (MEN1) -related tumors, and it was negative.

Standard X-ray images of target bones were taken (distal part of the left humerus with reduced bone density, in its proximal and middle parts were seen pseudocystic resorption zones, similar changes in distal part the right humerus and proximal right radius and ulna, reduced bone density of both femurs and right tibia).

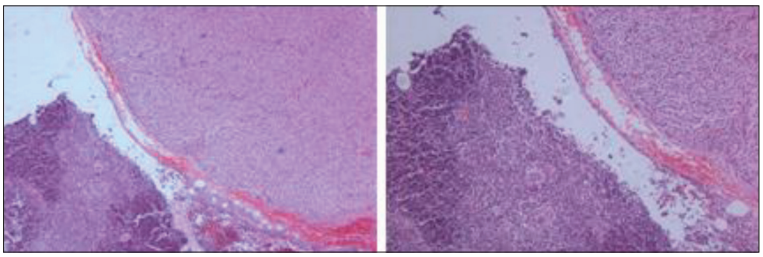

Figure 3. Final pathological section (50× and 100× magnified) – the nodule consisted of regular-looking parathyroid tissue surrounded by regular thymic tissue

Ultrasound of the neck was unspecific. Neck CT marked suspicious hyperplastic parathyroid tissue (5 mm) in the inferior aspect of the left thyroid lobe. Chest MRI showed some suspicious masses in close relation to both brachiocephalic trunks, which had characteristics of ectopic parathyroid tissue, lymphatic or fatty tissue.

^{99m}Tc-sestamibi scintigraphy including single-photon emission computed tomography study of the neck and mediastinum showed focal intensive uptake in the anterior part of the right mediastinum, which refers as ectopic adenoma or parathyroid gland hyperplasia (Figure 1).

Initially, the patient was treated conservatively with saline rehydration and diuretics, once with bisphosphonates infusion, and vitamin D supplements. Calcium level was normalized preoperatively.

After consultations with endocrinologists, adult general surgeons, otolaryngologist, adult thoracic surgeon and pediatric cardiothoracic surgeon, minimally invasive surgery was planned. The original plan included preoperative low dose methylene blue infusion, which should have accumulated into the ectopic parathyroid tissue and stained it blue. Unfortunately, intravenous methylene blue solution in our country was not available. Our decision was to perform surgery without intraoperative adenoma marking on. Intraoperative PTH levels monitoring and intraoperative localization with hand-held gamma counter probe were technically impossible as well. At last, frozen section biopsy was planned as intraoperative confirmation of parathyroid tissue removal.

Video-assisted thoracoscopy was performed under general anesthesia with supine positioned patient. Camera port of 5 mm was located in the fifth right intercostal space in the midaxillary line. Two working 5 mm ports were placed into the fourth and sixth right intercostal space in the anterior axillary line. A single suspicious mass was extirpated, but frozen section confirmed presence of regular thymus parenchyma and reactive lymph node inside the fatty tissue, without parathyroid tissue. Total thoracoscopic thymectomy was performed (Figure 2). Resected thymus had dimensions 10 × 4 × 3 cm and weighed 34.4 g. The capsule was thin and smooth. On cut surface, the regular thymic tissue was grayish to whitish, elastic, soft, lobular. In the upper pole of the right lobe, there was a well-circumscribed and encapsulated whitish nodule measured 11 × 4 mm. After removing the thymus, detailed exploration was repeated, and again no suspicious ectopic parathyroid tissue was found. Chest tube was placed, and lung re-expanded. There were no intraoperative complications and neat hemostasis was achieved.

Blood samples were collected at the beginning of the surgery, 10 minutes after removing the thymus, as well as 12 and 24 hours postoperatively. These results, which we could not get until the next day, showed that PTH levels

decreased down to normal (35.6 pg/ml after 10 minutes and 33.1 pg/ml after 12 hours), as well as calcium levels.

Final pathological section confirmed ectopic parathyroid adenoma, surrounded by regular thymic tissue (Figure 3).

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines.

Considering that our patient was a minor, all the data was published after obtaining parental consent.

DISCUSSION

PHPT has bimodal distribution in pediatric population. In newborns, this genetic condition is usually presented with all four glands hyperplasia. Another peak is in older children and adolescents, and is usually caused by single parathyroid adenoma (80%) [3–6]. Parathyroid carcinoma is extremely rare cause in children [7].

In approximately 15–80% of cases, ectopic mediastinal parathyroid tissue can be found inside the thymus [6, 8–12]. Inferior parathyroid glands and thymus both originate from the third pharyngeal arch [3, 6, 13]. Other common localizations of ectopic parathyroid tissue include mediastinum, thyroid gland, and parapharyngeal space [3, 9, 14–17]. Signs and symptoms of hyperparathyroidism can also be the first presentation of MEN1. This syndrome, beside parathyroid adenoma, includes intestinal-pancreatic endocrine tumors and pituitary tumors [13].

There are still no specific guidelines for precise preoperative localization of parathyroid tissue. Preoperative neck ultrasound facilitates spotting suspicious homogenous echoic nodule. This diagnostic tool is unable to detect mass which is not superficial, neither a mass which is behind air-filled structures. Also, masses that are located behind the sternum or generally in the mediastinum are not accessible. CT is not commonly used in children. MRI is a safe and non-invasive diagnostic imaging modality which can be used to detect suspicious ectopic nodules inside the mediastinum. Its disadvantages include poor differentiation between parathyroid tissue and lymph nodes [1]. The method of choice for localization of ectopic parathyroid tissue is parathyroid scintigraphy [18].

In our case, results of used diagnostic tools were quite different. However, MRI and radioisotope scan both spotted suspicious ectopic parathyroid tissue inside the mediastinum, with slight difference in its precise localization.

Bilateral four-gland neck exploration was the most commonly used surgical technique for treating hyperparathyroidism [16]. Unilateral neck exploration is considered appropriate in asymptomatic patients with mild forms of PHPT [16, 19].

Open cervical approach (collar incision by Kocher) can also be used for mediastinal adenomas located in close relation to the aortic arch, or more cranially located masses [3, 16].

For masses located deeper inside the mediastinum, instead of standard open techniques such as thoracotomy, median sternotomy and manubriotomy, minimally invasive approaches are developed as well (video-assisted mediastinal surgery [13, 17] and video-assisted thoracoscopy [20–23]. It is considered a "first line" treatment option for patients with mediastinal parathyroid adenoma located deeper than the brachiocephalic vein [20].

Intraoperatively, it is sometimes really hard to distinguish ectopic parathyroid tissue from usually present lymphoid and fatty tissue. Techniques such as methylene blue staining, gamma probe counter, frozen section biopsy or PTH levels monitoring can help locating the right one [17].

In vivo, parathyroid tissue is seen as yellowish-brown colored. If blood appears inside the surgical field, surrounding fatty and lymphatic tissue stains in color very similar to parathyroid tissue, which could lead to misrecognition [17, 21].

Intraoperative tissue localization using methylene blue infusion is proven helpful in approximately 80% of cases. This technique was suspected to be associated with severe adverse effects, such as neurotoxicity, especially in patients using selective serotonin reuptake inhibitors. More thorough studies, where lower doses of methylene blue solutions were used (3.5 mg/kg instead of 5–7.5 mg/kg) have proved its safety and efficiency [24]. As previously mentioned, we were not able to provide methylene blue solution, nor Geiger counter handheld probe.

Monitoring PTH levels during the surgery could confirm whether parathyroid secreting tissue has been removed (at least 50% decrease) [10]. In our patient's case, blood samples for PTH levels were collected prior to the surgery, as well as 10 minutes after removing thymus. Postoperatively, samples were taken after 12 and 24 hours. Unfortunately, these results in our case could not be obtained until the next day, so this technique did not provide us with sufficient information intraoperatively.

Practically, frozen section biopsy was the only available intraoperative monitoring. After removing the suspicious mass, which frozen section confirmed parathyroid tissue absence, we had to consider other surgical options. Knowing that the majority of mediastinal ectopic parathyroid adenomas can be found inside the thymus, our "plan B" was to perform thoracoscopic thymectomy.

There are numerous articles reporting of finding ectopic parathyroid tissue adenoma inside the thymus, as well as fewer complications in patients that were thymectomized during the initial surgery [25–28].

The final pathology report has confirmed ectopic parathyroid adenoma tissue inside the thymus, so we have avoided recurrence, consequent re-operation, and potential complications [25–28].

Postoperative revision of previously performed MRI scans was still inconclusive for precise mediastinal tumor localization.

Instead of a conclusion, we would like to underscore that if no parathyroid tissue is found during surgical exploration for parathyroid adenoma preoperatively localized in anterior mediastinum, recommendation is to think about possible intrathymic localization and consider removing the thymus. Greater sample size is necessary for higher reliability of this statement.

Conflict of interest: None declared.

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Видеоасистирана торакоскопија у случају примарног хиперпаратироидизма са аденомом локализованим унутар тимуса

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САЖЕТАК

Увод Примарни хиперпаратиреоидизам редак је у дечјем узрасту (2–5 : 100.000). Код преко 85% болесника присутан је аденом и његова екстирпација доводи до излечења. Код око 15–80% случајева ектопично ткиво паратиреоидне жлезде може се пронаћи унутар тимуса.

Приказ болесника Наш болесник био је тринаестогодишњи дечак, који је у клиничкој слици имао мултипле преломе и малаксалост. Вредности паратиреоидног хормона су преоперативно биле екстремно повишене (1320 *pg/ml* – преко 19 пута више од референтних). Вредности серумског калцијума су такође биле повишене (укупни 3,55 *mmol/l*; јонизовани 1,41 *mmol/l*). Педијатри ендокринолози су поставили дијагнозу примарног хиперпаратиреоидиза. После начињене преоперативне дијагностике, резултати сцинтиграфије и магнетне резонанце указивали су на постојање ектопичног медијастиналног паратиреоидног аденома. Урађена је видеоасистирана торакоскопска тимектомија, јер после детаљне експлорације медијастинума ектопично паратиреоидно ткиво није пронађено. Дефинитивни патохистолошки налаз потврдио је присуство паратиреоидног аденома унутар тимуса.

Закључак Уколико се током експлорације медијастинума код болесника са преоперативно доказаним ектопичним паратиреоидним ткивом у медијастинуму исти не пронађе, препорука је узети у обзир могућност његове локализације унутар тимуса, те размотрити тимектомију као начин хируршког решавања. Неопходно је истраживање на већем узорку како би се утврдила поузданост ове тврдње.

Кључне речи: примарни хиперпаратиреоидизам; видеоасистирана торакоскопија; тимектомија; сцинтиграфија паратиреоидних жлезда; деца

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Developmental hypomineralization of the enamel of the first permanent and the second deciduous molars – report of two cases

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SUMMARY

Introduction Molar-incisor hypomineralization (MIH) is a developmental defect of dental enamel that affects one to all four first permanent molars (FPM) and frequently permanent incisors. Enamel aberrations are observed as demarcated opacities of different colors (from white to brown) and as posteruptive enamel breakdown. Clinically similar pathological signs can also be present in deciduous molars.

Case outline Histology of an FPM and a second deciduous molar was performed after extraction from two unrelated patients with MIH due to inflammatory complications. Tooth samples were analyzed using a stereomicroscope (SM), light microscope (LM), and scanning electron microscope (SEM). Enamel thickness of both affected teeth was normal. An obvious distinction in enamel microstructure was observed between the normally developed and the molar-incisor hypomineralized enamel with SM, LM, and SEM.

Conclusion In MIH patients, regular dental visits enable early diagnosis of the disease and appropriate treatment of the patient as soon as possible, with included preventive measures.

Keywords: MIH; enamel; first permanent molar; second deciduous molar; histology

INTRODUCTION

Molar-incisor hypomineralization (MIH) is a distinct entity, with a typical clinical picture of developmentally impaired enamel. One to all four first permanent molars (FPM) are affected, as well as, in many cases, permanent incisors [1]. On individual teeth, enamel hypomineralization can be expressed in a wide variety in each patient [2]. The area of insufficiently mineralized enamel is clearly delineated from the normal enamel. Aberrant enamel of normal thickness can be of different colors, from whitish to brownish. Enamel mineralization can be insufficient to such an extent that the loss of enamel tissue occurs after the eruption of the tooth. Such areas of missing enamel are clinically identified as posteruptive enamel breakdown (PEB). As a rule, PEB is present on FPM. The size and the shape of such defects differ from carious lesions. PEB defects are present on areas where the carious process is not normally expected [3]. Because of the atypical location of deteriorated hypomineralized enamel, the shape of the filling on the MIH tooth does not coincide with the shape of a demineralized lesion that would develop due to caries. In patients with missing FPM that do not coincide with the clinical picture (the remaining teeth are healthy, with no caries or with only minor carious pathology), or in the presence of hypomineralized signs of MIH and/or atypical fillings on the remaining FPMs, the possibility that FPM was extracted due to MIH should also be considered.

Except for FPM and permanent incisors, signs similar to MIH are also described on the second deciduous molar (SDM), the second permanent molar, and incisal part/cusps/tips of the permanent canine [3]. Garot et al. [4] pointed out that children with MIH-like affected SDM have almost a five-fold higher likelihood of MIH presence in permanent dentition. The study aimed to describe macro- and micro-aberrations in the enamel of the FPM and the SDM obtained from two unrelated patients diagnosed with MIH.

CASE REPORT

Clinical examination of the patients

A nine-year-old boy was referred to the University Dental Clinic due to complications related to the endodontic treatment of a non-vital upper left FPM (tooth 26). The patient was otherwise healthy, with no metabolic, endocrine or any other systemic disease. The likelihood of dental fluorosis was excluded. The clinical status is described under Figure 1. The final interdisciplinary treatment plan was agreed upon. Based

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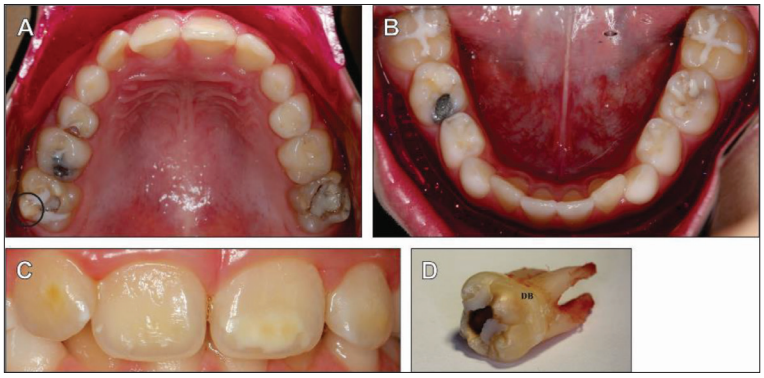


Figure 1. A) Upper dental arch of the nine-year-old boy with severely affected enamel of both upper first permanent molars (FPMs); on tooth 16, a hypomineralized disto-buccal tooth cusp (present in Figure 3) is marked with a circle; B) lower dental arch with healthy FPMs without hypomineralizational aberration; C) molar-incisor hypomineralization-affected permanent upper incisors; D) the extracted upper right FPM (tooth 16) with posteruptive enamel breakdown due to exceptionally poor mineralization of the enamel; DB – disto-buccal side of the tooth

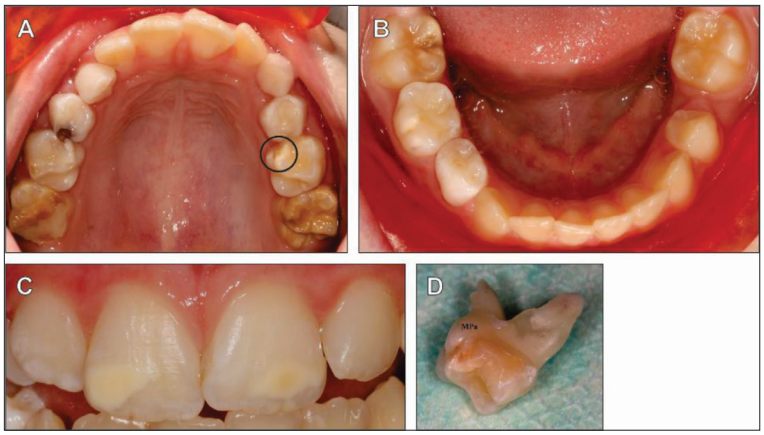
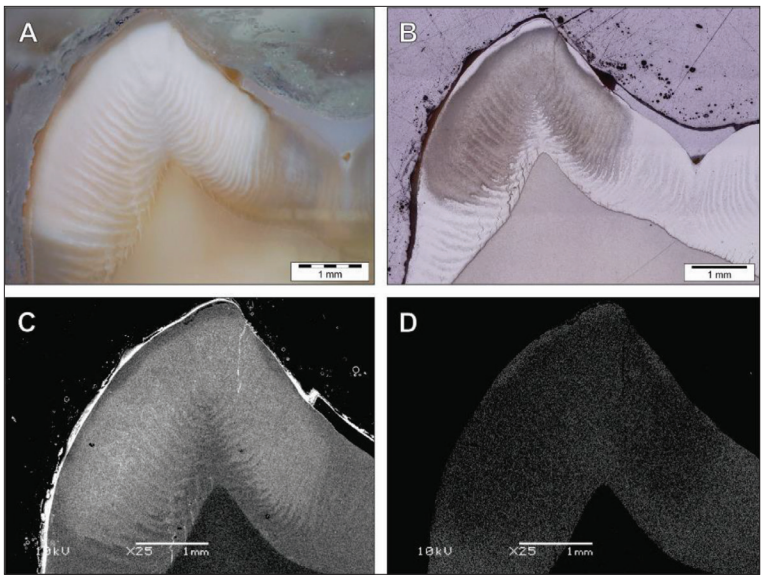


Figure 2. A) Nine-year-old girl with mixed dentition and severely affected enamel of both upper first permanent molars (FPMs); the right FPM with an atypical restoration and the left FPM (tooth 26) with posteruptive enamel breakdown; on tooth 65, a hypomineralized mesio-palatal tooth cusp (present in Figure 5) is marked with a circle; B) on the lower right FPM (tooth 46), insufficiently mineralized enamel is sharply demarcated from a normally developed enamel; deciduous molars have chalky-whitish patches (teeth 54, 55, 65, 84, and 85); two deciduous molars are missing due to premature extractions; C) both upper central incisors are also molar-incisor hypomineralization-affected; D) the hypomineralized upper left second deciduous molar (tooth 65), extracted due to recurrent spontaneous pulpitic pain and further histologically examined; MPa – mesio-palatal side of the tooth



on the results of the analysis of occlusal relations, the poor long-term prognosis of both upper FPMs and a possible midline shift, the decision to extract both upper FPMs was made. Tooth 16 (Figure 1C) was analyzed as described below.

The second patient, a nine-year-old girl, was referred to the clinic due to severe hypersensitivity of the upper right FPM (tooth 16). Her medical history also reported no systemic disease or medications (e.g., antibiotics, fluorides). The clinical status is described under Figure 2.

For the proposed treatment of the patients and further examination of the extracted teeth, informed consent was obtained from the patients and their parents. The study was approved by the Slovenian Committee for Medical Ethics (65/05/14).

Tooth samples

The analyzed teeth were MIH-affected FPM and MIH-like SDM, as described above. Upon extracting the FPM and the SDM, the teeth were placed in an isotonic saline solution and then cut in the bucco-palatal direction. Both halves of each tooth were embedded in epoxy resin (Araldite, Ciba-Geigy, East Lansing, MI, USA) and polished after 24 hours, according to the established laboratory protocol. These prepared tooth specimens were examined in relation to histology with a stereomicroscope (SM), light microscope (LM), and scanning electron microscope (SEM).

Stereo microscopy, light microscopy, and scanning electron microscopy

Initially, the samples' enamel histology was observed with SM (Olympus SZ61, Olympus, Tokyo, Japan), LM (Olympus

Figure 3. A) Stereo microscopy and B) light microscopy of the longitudinally cut upper-right first permanent molar (tooth 16) crown showed clearly less mineralized enamel through most of its thickness of an molar-incisor hypomineralization-affected disto-buccal tooth cusp; between the porous and normally mineralized enamel, a clear delineation is visible; C, D) the same distobuccal tooth cusp observed with a scanning electron microscope; C) on the secondary electron image directly below the surface, a thin layer (of some ten micrometers in its width) of appropriately mineralized enamel and a ribbon of normally mineralized enamel near the dento-enamel junction are visible; hypomineralized areas of enamel are brighter compared to apparently normal enamel; D) on the backscattered electron image, hypomineralized areas of the enamel appear darker, and the borders are not as distinct as on the secondary electron image

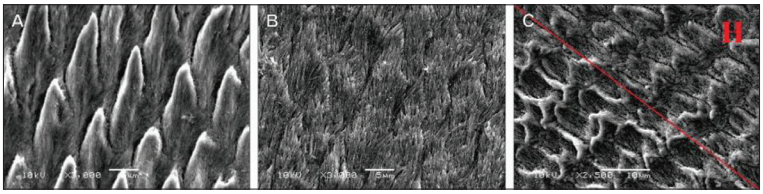


Figure 4. Scanning electron microscopy of an etched sample of the affected first permanent molar presenting A) normal and B) aberrant areas of the enamel; A) on parts where the course of amelogenesis was normal, the appearance of enamel prisms is typical, with nicely arranged enamel prisms; hydroxylapatite crystals are closely packed and correctly oriented (secondary electron image – SEI, ×3000); B) conversely, on hypomineralized parts of the enamel, enamel prisms are less prominent; hydroxylapatite crystals are not packed together so tightly (SEI, ×3000); C) image presents the sharp delineation (delimited with red line) between the porous [i.e., hypomineralized, marked with H, and normally mineralized enamel (SEI, ×2500)]

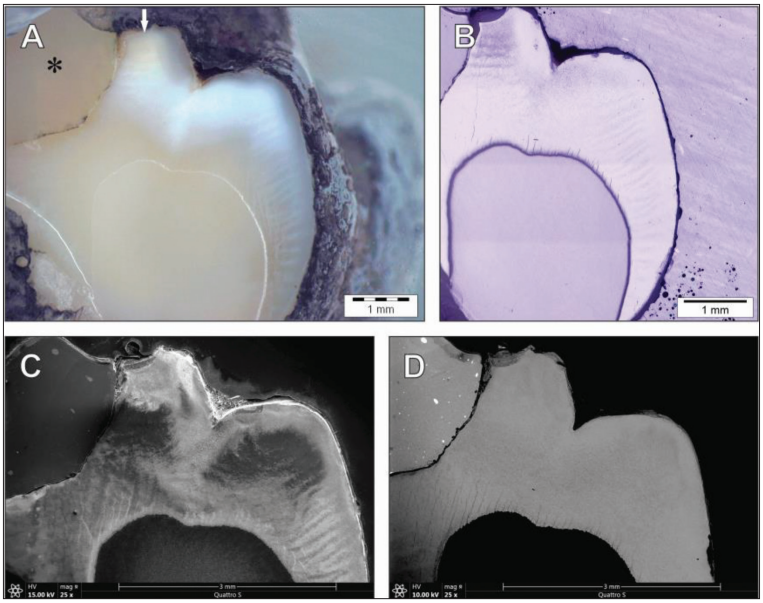


Figure 5. Longitudinally cut upper-left second deciduous molar (tooth 65), observed as an unetched specimen with A) stereo microscopy and B) light microscopy, revealed insufficiently mineralized enamel through the most of enamel thickness of the affected mesio-palatal tooth cusp; note a clear delineation between the insufficiently and normally mineralized enamel; the majority of the opacity is whitish, more porous hypomineralized enamel adjacent to the filling (marked with an asterisk) is cream-colored (indicated by an arrow); the same tooth cusp, observed with a scanning electron microscope, after previous etching for 20 seconds, shows C) two layers of normally mineralized enamel: a layer directly below the enamel surface and a layer near the dento-enamel junction (DEJ); the layer near the DEJ is slightly wider than the layer near the DEJ observed in the first permanent molars (secondary electron image); D) observation with backscattered electrons exposed no obvious differences in the enamel structure

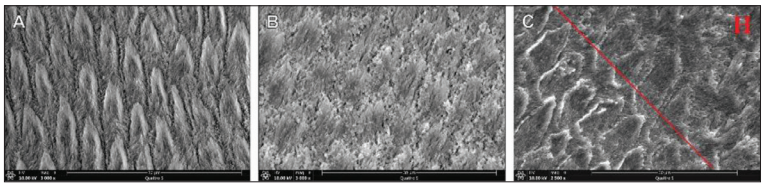


Figure 6. Scanning electron microscopy of the etched sample of the affected second deciduous molar present A) typical etching pattern of properly arranged and well-formed enamel prisms in an area with normally developed enamel; hydroxylapatite crystals are closely packed and correctly oriented (secondary electron image – SEI, ×3000); B) conversely, in the cream-colored area of the enamel, the prisms are disorganized (SEI, ×3000); C) the red line on the image shows clear demarcation in the histological structure of porous (H) and normally mineralized enamel (SEI, ×2500); H – hypomineralized enamel

BX61, Olympus) at different magnifications. After the histological examination with SM and LM was completed, the tooth samples were prepared for SEM according to the established laboratory protocol. Non-etched and later-etched enamel samples (37% phosphoric acid) were observed with SEM (QuattroS, Thermo Scientific, Waltham, MA, USA).

Enamel histology

In both tooth samples, the thickness of the enamel was normal. However, both samples had areas with developmentary hypomineralization enamel, which extended almost all the way from the dento-enamel junction (DEJ) to the tooth surface (Figures 3 A–D and 5 A–C). A thin layer of unaffected enamel on the tooth surface was lined with a normal aprismatic layer, while the majority of the bulk of the enamel was altered to varying extents. Under the LM, the hypomineralization areas appeared darker. As shown in Figures 3 and 5, the surface of the MIH-affected tooth cusp could be preserved. In parts with regular development, the prisms were normal and well defined (Figures 4A and 6A). In the aberrant part of the enamel, the microstructure was deficient in most of its thickness, with prisms poorly defined and inadequately mineralized (Figures 4B and 6B). In areas with poorly formed or even unrecognizable enamel prisms, different levels of porosity is anticipated, as well as residual organic material which had not been removed during amelogenesis. On etched samples, the difference between the normally formed enamel (with a well-formed etching pattern) and the hypomineralized enamel (with prism boundaries not clearly delineated) was even more apparent. The microstructure of the hypomineralized enamel showed poorer organization of the hydroxyapatite crystals within the prisms and wider sheath regions.

In the FPM and the SDM, a clear demarcation between the normally developed and the developmentally affected enamel was observed under SM, LM, and SEM (Figures 4C and 6C). Furthermore, in both samples, hypomineralized areas seemed to follow the incremental lines of Retzius. In the FPM, as well as in the SDM, no changes in the structure of the dentine underneath the hypomineralized enamel was observable.

DISCUSSION

In this report, we observed poorly formed enamel prisms and insufficient mineralization of macroscopically MIH-affected enamel. Hypomineralized areas spread from the DEJ towards the surface of the dental crown. The results coincide with a publication on the typical histology findings in MIH-affected FPMs [5]. Regarding the extent of hypomineralization, aberrant areas may only be present in the inner layers of the enamel, at the DEJ, or may include almost the whole enamel thickness [6]. In the yellow-brownish MIH-affected enamel, the entire thickness of the enamel is usually affected [7]. If the surface of the crown remains intact, the surface of the enamel is better mineralized compared to the deeper layers of the enamel. This is attributed to the final mineralization of the enamel after the eruption of the tooth [6]. The porosity of hypomineralized enamel enables the penetration of bacteria into the dentin, although the tooth surface is clinically intact. The bacteria in the dentinal tubules provoke an inflammatory reaction in the pulp, which consequently contributes to the hypersensitivity of MIH teeth [8]. Hypomineralized molars are also more prone to caries than those without developmental impairment, can cause serious restorative problems, and often even need to be extracted due to the extent of developmental disruption and treatment complications [9].

In this study, obtained results of chalky-like whitish patches on SDM also confirmed a poorer histological structure and enamel hypomineralization. We observed an aberrant histology of the affected enamel, which is similar to a recently published article [10]. In both the FPM and the SDM specimens, there were clear demarcations between aberrant and normal enamel. However, the extent of hypomineralization was more severe in the FPM than in the SDM. This was not surprising since, as a rule, clinically MIH-like aberrations on SDMs are less severe than on FPMs [4]. A recently published systematic review of studies performed on extracted teeth diagnosed with MIH found a reduction in mineral quantity and quality in the MIH-affected enamel compared with unaffected enamel [11]. Furthermore, MIH-affected enamel showed less dense prism structure, loosely packed crystals, more marked inter-prismatic space, wider sheath regions, and abnormal etching pattern compared to normal enamel.

In conclusion, early diagnostics and proper treatment of the MIH-affected enamel is of the utmost importance. Especially in cases of severe MIH, the failure to diagnose the disease early or delaying the necessary treatment may lead to additional complications that can result in the loss of tooth vitality or even of a tooth. The predictive factor for MIH disease of non-erupted FPMs can also be clinically detected in the MIH-like developmental impairment of SDMs; not only those with PEB but also with demarcated chalky hypomineralization defects on the surface of its tooth crown.

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Развојна хипоминерализација глеђи првог сталног и другог млечног молара – приказ два болесника

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САЖЕТАК

Увод Хипоминерализација молара и инцизива развојно је оштећење зубне глеђи која погађа један до сва четири прва стална молара, а често и сталне секутиће. Аберације глеђи виде се као ограничена замућења различитих боја (од беле до смеђе) или као постеруптивни губитак глеђи. Слични клинички патолошки знакови могу бити присутни и на млечним моларима.

Приказ болесника Хистологија првог сталног молара и другог млечног молара изведена је након што су зуби екстраховани због запаљенских компликација код два болесника са хипоминерализацијом молара и инцизива. Хистологија зуба анализирана је уз помоћ стерео-микроскопа, светлосног микроскопа и скенирајућег електронског микроскопа. Дебљина глеђи оба оболела молара била је нормална. Уочена је јасна разлика у микроструктури глеђи између нормално развијене и хипоминерализоване глеђи са стереомикроскопом, светлосним микроскопом и скенирајућим електронским микроскопом.

Закључак Код болесника са хипоминерализацијом молара и инцизива редовни стоматолошки преглед омогућава рану дијагнозу болести и одговарајуће лечење пацијената у најкраћем могућем року, уз укључене превентивне мере.

Кључне речи: хипоминерализација молара и инцизива; глеђ; први стални молар; други млечни молар; хистологија

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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Local allergic rhinitis – a big challenge in clinical practice

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SUMMARY
Local allergic rhinitis is a new rhinitis phenotype characterized by symptoms similar to allergic rhinitis, in non-atopic patients with a positive nasal allergen provocation test (NAPT). The disease is diagnosed in over 25% of non-atopic patients with rhinitis, marked as non-atopic rhinitis. It most often has perennial and severe symptoms and a progressive course. It is often associated with conjunctivitis and/or asthma. It is necessary to consider local allergic rhinitis in patients with non-atopic rhinitis. The gold standard for diagnosis is a positive NAPT. Pharmacological therapy fails to stop the natural progression and development of comorbidities. Allergen immunotherapy reduces the symptoms, consumption of medicines and increases the tolerance to allergens responsible for local allergic rhinitis. New studies are needed to confirm the curative effects and evaluate the preventive effects of allergen immunotherapy.
Keywords: local allergic rhinitis; diagnosis; therapy

INTRODUCTION

Local allergic rhinitis (LAR) is a new rhinitis phenotype, defined and introduced into clinical practice by Campo et al. [1] and Rondon et al. at the end of the previous decade [2–4]. The base of LAR is a localized allergic reaction limited to the nasal mucosa, in the absence of systemic atopy. Patients have seasonal or perennial symptoms similar to allergic rhinitis (AR), without signs of atopy. To date, researchers have elucidated the etiology, underlying mechanisms, clinical features, and provided guidelines for the diagnosis and treatment. Most commonly, LAR has severe symptoms and progressive course, and is often associated with other inflammatory diseases, such as conjunctivitis and/or asthma. The continuous progression of the disease and poor response to pharmacological therapy significantly decrease the quality of life of these patients [5, 6, 7]. Considering that chronic rhinitis affects more than 30% of the population, of whom at least a quarter are patients with LAR, it is clear that this disease represents a huge financial burden on the health system. The characteristics of LAR impose the need for recognition, timely diagnosis, and effective treatment [8].

RHINITIS CLASSIFICATION

Rhinitis has been traditionally classified as infectious, non-infectious, and mixed rhinitis. This traditional classification of rhinitis is based on etiological criteria [8]. Non-infectious rhinitis is the most frequent chronic rhinitis, which divides into AR and non-allergic rhinitis (NAR). This division is also etiological and relies on the atopy characteristics: the presence of a positive skin prick test and/or allergen-specific IgE in serum. NAR is characterized by symptoms of chronic rhinitis, a negative skin prick test, and the absence of allergen-specific IgE in serum. NAR forms a heterogeneous group, divided into several phenotypes. The most important phenotypes with known etiology are drug-induced rhinitis, hormonal imbalance-induced rhinitis, occupational, gustatory, and rhinitis in the elderly. NAR of unknown etiology includes rhinitis with eosinophilia syndrome and idiopathic rhinitis. AR is a unique phenotype, which has characteristic symptoms and positive signs of atopy: skin prick test and/or allergen-specific IgE in serum. By isolating LAR, the traditional dichotomous division of non-infectious rhinitis has been "demolished." The recognition of this new phenotype of rhinitis, which does not have any sign of atopy, enabled its separation from NAR, where it was unjustifiably classified. In the new classification of non-infectious rhinitis, LAR is labeled as new AR phenotype and it is added to a group of AR, together with atopy AR. This change is of great importance. It allows patients with LAR to be recognized and treated more efficiently [8–11].

LOCAL ALLERGIC RHINITIS DEFINITION

LAR is a new and distinct rhinitis phenotype characterized by symptoms of AR, in patients with a negative skin prick test and the absence

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of serum-specific IgE directed to inhalant allergens, but with a positive nasal allergen provocation test (NAPT) [1, 2, 3]. Therefore, these patients do not have indicators of atopy [5]. The main cause of disease is allergic response to inhalant allergens restricted to the nasal mucosa. This is also called "entopia," which distinguishes these patients from patients with AR and atopy [10, 11, 12, 13].

EPIDEMIOLOGY

Non-infectious rhinitis is a global health problem, with a frequency exceeding 30% of the general population and of great medical, economic, and social importance [14]. Until LAR was recognized, it was estimated that approximately half of these patients had NAR, based on the absence of signs of atopy. With the knowledge that LAR also does not have signs of atopy, because it was not distinguished from NAR, these two groups of rhinitis were marked as non-atopic rhinitis. This has attracted a great deal of researchers' attention. Over the past decade, numerous epidemiological and clinical studies have indicated a high incidence of LAR in patients with non-atopic rhinitis, in the range of 50–75% [15]. Some studies indicate greater representation in the Mediterranean than in Northern Europe or in some Asian countries [16, 17, 18]. The most recent systemic and meta-analysis of selected studies indicates that the incidence of LAR in adults with non-atopic rhinitis is about 25%. The incidence is higher if positive NAPT is not the only criteria for diagnosis, but there are also symptoms suggestive of AR [19]. The prevalence in the elderly is estimated at 21% [20]. Despite this knowledge, there is an opinion that LAR is underdiagnosed, i.e., that a large number of these patients remain unrecognized [15, 20].

PATHOPHYSIOLOGY

The first evidence of exclusively local production of specific IgE in the nasal mucosa in individuals with non-atopic rhinitis was documented in 1975. In the nasal secretion of patients with symptoms of AR and negative outcome of allergic tests, Hugins and Brostof were the first to detect specific IgE directed to dust mites *Dermatophagoides pteronyssinus* [21]. Later, at the beginning of the 21st century, the infiltrates of IgE-positive cells in the nasal mucosa was also detected in individuals with atopic and non-atopic rhinitis [22]. Following the isolation of LAR, a new term "entopia" was introduced to highlight the basic feature of the new rhinitis phenotype, exclusively the local synthesis of specific IgE in the nasal mucosa [12].

The underlying pathophysiological mechanism of LAR is anaphylactic hypersensitivity, mediated by helper T lymphocytes, cytokine phenotype 2, and allergen-specific IgE directed to common inhaled allergens. A direct consequence of the allergic response, triggered by environmental allergens, is the development of type 2 inflammation, restricted to the nasal mucosa [23, 24, 25]. After natural exposure to allergens from the external environment or after NAPT, there is a transient increase in tryptase concentration and a progressive increase in the concentration of specific IgE, the number of eosinophils and the eosinophil cationic protein in the nasal secretion. The allergic inflammation thus originated has all the features of eosinophilic inflammation and a similar cell phenotype to that of AR. Allergic inflammation in both cases is characterized by a high content of eosinophils, basophils, mast cells and helper lymphocytes T, cytokine phenotype 2 [23, 26].

In subjects with AR, local synthesis of specific IgEs, after exposure to environmental allergens, is potent, rapid and results in complete sensitization of nasal mucosal effector cells. Specific IgEs bind to their high-affinity receptors on a number of resident effector cells (mast cells, eosinophils, T and B lymphocytes) with Fc fragment. However, a large portion of locally synthesized specific IgE remains free, enters the systemic circulation, and sensitizes circulating basophils and subsequently other resident cells, such as skin mast cells and other cells. After the saturation of high-affinity receptors on the resident cells of numerous tissues and organs, a free fraction of specific IgE appears in the serum [14, 27].

Unlike AR, there is no direct evidence that the same process occurs in patients with LAR. In these individuals, it is assumed that locally synthesized specific IgEs, after saturation of the high-affinity receptors on resident cells of the nasal mucosa, enter the systemic circulation only to a small extent. The systemic fraction of specific IgE sensitizes circulating basophils but no other resident cells, nor does it appear as a free fraction in serum. In support of this assumption is the positive outcome of a basophil activation test and a positive response to allergen immunotherapy (AIT) in patients with LAR [28, 29, 30].

Despite pathogenetic similarities, the precise pathophysiological mechanisms and role of specific IgEs in LAR are still insufficiently known. It remains unclear why most patients with symptoms of AR develop systemic sensitization (atopy), while a far smaller number develop only a local allergic response [31].

CLINICAL CHARACTERISTICS

LAR is an isolated, independent, and well characterized rhinitis phenotype. The most commonly affected individuals are young adults, in whom disease has a chronic course with a tendency to worsen. Patients most often have perennial, moderately severe to severe rhinitis that is difficult to control [14–18]. Dust mites and molds are major causes [32]. One of the main features of this rhinitis phenotype is its independence. In a large study by Rondon et al. [7], a 10-year follow-up of over 190 adolescents and adult subjects with LAR recorded a low conversion rate to atopic AR. This conversion rate did not differ from the general population. This confirmed the independence of this phenotype with evidence that LAR is not an initial stage in the development of atopic AR. Regardless of the age at which it occurs, it always has a progressive course that leads to a continual exacerbation of the disease. The exacerbation is manifested by the following: worsening of symptoms with extension of

their duration and a greater need for medication, a decrease in the tolerance threshold for allergen exposure, the emergence of new local sensitizations and comorbidities, most commonly conjunctivitis and asthma. The most intense period of exacerbation is the first five years of the disease [7]. An inevitable consequence of such a clinical course is a decrease in the quality of life of these patients. A typical patient with LAR is a younger non-smoker, who has perennial rhinitis, often associated with symptoms of conjunctivitis and asthma. Compared to patients with NAR, these patients are significantly younger, with more severe symptoms and a positive family history of atopy [15].

LOCAL ALLERGIC RHINITIS AND ASTMA

Some studies by Spanish authors indicate that LAR is a risk factor for asthma in non- atopic individuals [33, 34]. These patients often have symptoms associated with the lower respiratory tract indicating asthma. It is estimated that 20–47% of patients report typical asthma symptoms, while half of patients have a positive methacholine test and a confirmed diagnosis of asthma. The association of LAR with asthma has been observed at the outset of the disease, and this association has steadily increased over time, with a tendency to exacerbate asthma symptoms and pulmonary function [7, 34]. This conclusion is also indicated by the results of a large and to date the only long-term, 10-year follow-up study of patients with LAR. In this study, less than 19% of patients with associated asthma symptoms were registered at the onset of the disease; after 10 years, the incidence increased to over 30%. The fastest and the highest rate of progression to asthma was during the first five-year period of the disease. There was also a significant increase in emergency room interventions, physician visits, and impaired pulmonary function. This study confirms the natural, progressive course of LAR and its association with asthma [7]. The nature of this close association has been the subject of intense research in recent years. Recent studies show that as many as 28% of patients with LAR, due to hypersensitivity to dust mites and confirmed asthma, have a positive outcome of specific bronchoprovocation test with *Dermatophagoides pteronyssinus*, followed by worsening asthma and increased non-specific bronchial hyperreactivity. Analysis after the test showed a significant increase in the number of eosinophils, monocytes, and the concentration of eosinophilic cationic protein in induced sputum, but not in peripheral blood. The cell content did not differ from that in allergic asthma. This finding indicates that the development of eosinophilic inflammation in the bronchial mucosa is the basis of asthma, in patients with LAR [34]. This is a direct confirmation of the existence of allergic asthma in persons with non-atopic constitution. The results of this study reinforce the earlier findings of local synthesis of specific IgE in bronchial mucosa, as well as the increase in IgE concentration in induced sputum after a specific bronchoprovocation test in patients with non-atopic asthma [33, 34]. These studies confirm that etiology of asthma in patients with LAR is a localized allergic inflammation of the bronchial mucosa. For these reasons, asthma in these patients has been called local allergic asthma, in an effort to isolate a new phenotype of allergic asthma in individuals with non-atopic constitution [34]. These findings further confirm the concept of united airway diseases, by unequivocal evidence of the pathophysiological connection between LAR and local allergic asthma [35–39].

LOCAL ALLERGIC RHINITIS AND CONJUNCTIVITIS

Patients with LAR often experience itching in the eyes, redness, and increased tearing. Eye symptoms are more common in patients with local sensitization to various pollen species than in those with local sensitization to household dust mites. In these patients, the presence of IgE in tears was demonstrated, which prompted a group of Japanese researchers to suggest a new term – local allergic conjunctivitis. A large number of mast cells, T and B lymphocytes, are present in the epithelium of the conjunctiva, and in allergic conjunctivitis there are resident B cells that synthesize specific IgE that sensitizes mast cells in the conjunctiva. However, it is still unclear whether ocular symptoms in LAR are due to local sensitization of the conjunctiva or activation of the naso-ocular reflex, after exposure of the nasal mucosa to inhaled allergens [40].

DUAL ALLERGIC RHINITIS

Following the discovery of LAR, its association with AR and coexistence in the same atopic person was observed. This phenotype is called dual allergic rhinitis. It is characterized by the presence of symptoms of AR, that are consequence of both local sensitization of the nasal mucosa i.e., entopic to certain allergens and systemic sensitization, i.e., atopy to other inhalation allergens. The number of these patients in clinical practice is not negligible, and trials are yet to define this latest rhinitis phenotype more closely [41, 42].

LOCAL ALLERGIC RHINITIS IN CHILDREN

A significant number of adolescents and adults with LAR associate their first symptoms with childhood. For these reasons, a number of studies indicate the need to include LAR in a differential diagnosis in children with chronic rhinitis. This remark is justified by the systematic analysis of several studies on over 250 pediatric patients with suspected LAR with a prevalence of positive NAPT of 16.1% [15]. Recent studies conducted on nearly 400 pediatric patients, some of whom with multiple NAPT, confirm LAR in a wide range of 37–67% of children. The highest incidence is in western countries, with the often-associated atopic dermatitis and conjunctivitis as the most common comorbidities. The evolution and clinical characteristics of LAR in children are still under investigation [43, 44, 45].

DIAGNOSIS

LAR should always be considered in patients with symptoms of AR, but without evidence of atopy. Recognition and early diagnosis are crucial for the timely introduction of therapy, symptom control, and comorbidity prevention. Diagnostic procedure involves a detailed patient history and examination, tests to prove atopy and allergic response of the nasal mucosa, provident their correlation with natural allergen exposure and exclusion of other potential causes of rhinitis [1, 3, 5, 9–12]. The history and examination of patients suspected to LAR is characterized by the symptoms and the look of patient that are characteristic of AR. However, these patients do not have a positive skin prick test nor specific serum IgE to common inhaled allergens. When there is doubt, other causes of rhinitis should be ruled out. The gold standard for the diagnosis of LAR is NAPT with selected allergen (or allergens) suspected to be responsible for the onset of the symptoms. People with a negative outcome of NAPT definitely have NAR. A positive outcome of NAPT indicates that the allergen that triggers allergic inflammation in the nostril mucosa under laboratory conditions is responsible for the symptoms of the disease. The connection of symptoms in positive NAPT with natural exposure to the same allergens clearly confirms that the given allergen is responsible for LAR [1, 5, 25, 41, 44, 46]. NAPT is characterized by high sensitivity, specificity, and reproducibility. The performance of this test should be entrusted to trained personnel in specialized institutions using standardized protocols. Under these conditions, performing NAPT is safe and reliable [43, 46]. In recent years, protocols have been developed to perform two or more NAPT at a single visit to a diagnostic unit, thus shortening diagnosis [7, 40]. Testing concentration of specific IgE in the nasal secretion and a basophil activation test were also developed. However, the low sensitivity of these assays and poor reproducibility still precludes their routine application [5, 44].

THERAPY

Contemporary therapy of LAR is based on well-known strategies for treating AR, relying on the immune and clinical similarities of these two phenotypes [1, 5, 47, 48]. Considering that avoiding causative allergens is difficult to implement in practice and that there are no official recommendations for AIT, treatment relies on patient education and pharmacological therapy. The goal of therapy is to control the symptoms and prevent disease progression.

To date, there are no studies evaluating the efficacy of leading controllers, oral antihistamines, and intranasal corticosteroids in LAR. Experience indicates a similar short-term effectiveness of these drugs in the control of AR and LAR [5, 9, 13]. However, more recent studies, with long-term monitoring of the effectiveness of pharmacological therapy, show different results. In patients with LAR, in a 10-year period, there was a significantly increased need for oral and intraocular antihistamines with a progressive increase in the use of intranasal and oral corticosteroids. At the same time, there was a worsening of symptoms, decreased tolerance to allergens responsible for the symptoms, and development of associated asthma symptoms. The results of a long-term trial show that pharmacological therapy, however, fails to control the symptoms and stop the natural progression of LAR, exacerbation, and development of comorbidities, primarily asthma [1, 8].

The similarity between LAR and AR phenotype and the proven efficacy of AIT in AR, have led researchers to apply AIT in LAR. Regardless of the absence of official recommendations, AIT was chosen as the best choice to the naturally progressive course of LAR. The experience is based on a total of four studies evaluating the short-term, clinical, and immunological effects of subcutaneous immunotherapy (SCIT) in LAR. All four studies were conducted using standardized allergen extracts, one observational and three randomized, double-blind, placebo-controlled studies, on a total of 140 subjects [2, 27, 28, 29].

The first study and the first official administration of AIT in LAR, was published by Rondon et al. [27] in 2011. They conducted an open-label, observational study, in patients with moderately severe seasonal LAR due to grass pollen hypersensitivity. In this study, they demonstrated that SCIT with a grass pollen mixture in the preseason protocol (six months), has beneficial clinical and immunological effects. Subjects who underwent SCIT had significantly fewer symptoms and lower drug consumption compared to the pre-SCIT season. These patients also achieved a significantly greater number of medication-free days than the control group, treated only with pharmacological therapy. During SCIT, patients significantly increased the tolerance of the nasal mucosa to the grass pollen. Clinical effects were accompanied by a significant increase in serum-specific immunoglobulin G4 (IgG4) concentration [27]. Although these results were impressive, the value of the study significantly diminishes its experimental design. For this reason, the same group of authors subsequently published two randomized, controlled studies, focusing on the clinical and immunological effects of SCIT in seasonal and perennial LAR. The results of these studies show that the two-year of SCIT with allergenic extract *Phleum pratense* in seasonal and *Dermatophagoides pteronyssinus* in perennial LAR also had beneficial clinical and immunological effects. Subjects receiving SCIT significantly reduced the combined symptom drug score, with significant increase of medication-free days and nasal mucosal tolerance to grass pollen and *Dermatophagoides pteronyssinus*. After the SCIT termination, as much as 50% of the treated patients tolerated maximum concentrations of allergens in laboratory conditions when performing NAPT. Beneficial clinical effects have been confirmed by improving the quality of life of these patients. The overall clinical effects of SCIT were also accompanied by a significant increase in specific IgG4 concentration in the serum [2, 28]. Similar effects of SCIT in LAR were confirmed in the randomized clinical study by Bozek et al. [29].

CONCLUSION

The rejection of the traditional conception of equalization of the allergic etiology of rhinitis with atopy changed the understanding and approach to patients with non-atopic rhinitis. The outcome of this change is LAR, the discovery of which was undoubtedly a major step forward in allergology at the beginning of the 21st century. Unfortunately, due to the low availability of NAPT in clinical practice, many cases remain unrecognized. It is necessary to include NAPT in the diagnostic algorithm of chronic rhinitis as soon as possible, as well as to better equip diagnostic units of airway allergic diseases. The disease has a progressive course, tends to worsen, cause the comorbidities and poor response to pharmacological therapy. The experience gained with AIT is positive and encouraging. Therefore, there is optimism that this causal therapy has the ability to slow and/or stop the progressive course of LAR and facilitate the disease control. New studies are needed to confirm existing curative effects and to evaluate the long-term preventive effects of AIT. LAR remains a major challenge for all physicians dealing with allergic airway diseases.

Conflict of interest: None declared.

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Локални алергијски ринитис – велики изазов у клиничкој пракси

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САЖЕТАК

Локални алергијски ринитис је нови фенотип ринитиса који се одликује симптомима сличним алергијском ринитису, без показатеља атопије али са позитивним специфичним ринопровокационим тестом. Болест се дијагностикује код преко 25% неатопијских пацијената са ринитисом, названим неатопијски ринитис. Најчешће има перенијалне и изражене симптоме и прогресиван ток. Често је удружен са конјуктивитисом и/или астмом. Локални алергијски ринитис треба обавезно размотрити код особа са неатопијским ринитисом. Фармаколошка терапија не успева да заустави прогресију и развој коморбидитета. Алергенска имунотерапија умањује симптоме, потрошњу лекова и повећава толеранцију на алергене одговорне за локални алергијски ринитис. Потребне су нове студије које ће потврдити постојеће и проценити превентивне ефекте алергенске имунотерапије.

Кључне речи: локални алергијски ринитис; дијагноза; терапија

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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Oral changes in patients before and after transplantation of solid organs and hematopoietic stem cells

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SUMMARY

Introduction/Objective The aim of this paper is to point out the prevalence and severity of oral diseases in patients in the period before and after the transplantation of solid organs and hematopoietic stem cells.

Methods MEDLINE literature search was done via PubMed.

Results The development and improvement of transplantation medicine in specialized centers lead to an increasing number of patients, both adults and children, with transplanted solid organs and hematopoietic stem cells. Despite the success of therapy, numerous changes and complications can be observed on other organs in patients undergoing transplantation of solid organs and hematopoietic stem cells in the pre- and post-transplant phase. Systemic diseases and conditions related to organ and cell transplantation, which are accompanied by numerous oral manifestations. The most common oral changes are gingival enlargement, desquamation of the oral epithelium, very painful ulcerations, polypoid and granulomatous changes in the oral mucosa, hard dental tissues with frequent complications, developmental anomalies of teeth in younger children, and in the later stage also the occurrence of oral cancer. After transplantation of solid organs, hematopoietic changes in the oral cavity and other organs occur depending on the patient's post-transplantation period as well as on the applied immunosuppressive therapy.

Conclusion Oral changes development before and after transplantation of solid organs and hematopoietic stem cells point to the importance of timely and competent cooperation between the dentist and the doctor who treats the underlying disease.

Keywords: organ transplantation; hematopoietic stem cell transplantation; oral diseases

INTRODUCTION

Transplantation of solid organs is a mostly surgical therapeutic method by which the non-functioning organs are replaced with healthy ones. It is applied in treatment of various diseases that lead to permanent damage to the function of certain organs. Transplantation of hematopoietic stem cells is most frequently carried out in the treatment of the most severe forms of hematological diseases and some forms of malignant tumors. Transplantation of solid organs and hematopoietic stem cells is a demanding and complicated process that requires the engagement of a multidisciplinary team. For the success of this procedure, a comprehensive preoperative and postoperative management of the patient is extremely important. Owing to significant discoveries in the field of transplantation medicine, as well as comprehensive multidisciplinary treatment of patients in the peritransplantation period, long-term survival without symptoms of the basic disease is enabled. Transplantation of solid organs and hematopoietic stem cells significantly influenced the length and quality of life of patients [1].

In patients with transplanted organs and cells, despite the success of the therapy, numerous changes can be observed on other organs and systems. The risks and adverse effects of transplantation on other organs occur depending on the duration of the underlying disease, general state of the organism, the presence of another chronic illness, the applied therapy, or the age of the patient. These changes can be diagnosed in the pre- and post-transplant phase. Changes affecting soft and hard tissues of the oral cavity are among the most widespread changes. The most common oral changes include gingival enlargement, periodontal diseases, desquamation of the oral epithelium, very painful ulcerations, polypoid and granulomatous changes in the oral mucosa and in the later stages, as well as the occurrence of oral cancer [2, 3]. Due to the extensive accumulation of oral biofilm and the presence of mineralized deposits on the teeth, these patients are also suffering from diseases of hard tooth tissues with frequent complications. Changes in the form of obliteration and calcification can occur in the pulp cavity. In children, where the processes of odontogenesis have not yet been completed, developmental anomalies of hard dental tissue may occur. These anomalies are more pronounced and more frequent in younger children in early stages of odontogenesis. Hypoplastic enamel changes, delayed tooth eruption, endogenous

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changes in tooth color, as well as changes in the development of the roots of primary and permanent teeth are the most commonly occurring anomalies [4–7].

After transplantation of solid organs and hematopoietic stem cells, changes in the oral cavity and other organs occur depending on the transplantation period in which the patient is as well as on the applied immunosuppressive therapy. Due to frequent oral diseases in the peritransplant period, dentists are an important part of the multidisciplinary team participating in the care of patients in all major transplant centers in the world. Dental treatment is an integral part of the transplantation protocol in these centers, both during the preparation period and after transplantation [1, 8].

The most numerous are patients with transplanted cells, that is – hematopoietic stem cells, followed by patients with kidney and liver transplants, in regard to solid organ transplantation.

SOLID ORGAN TRANSPLANTATION

Numerous chronic kidney diseases represent major health problems all over the world. A progressive decrease in renal function or organ failure is usually a consequence of various chronic diseases that lead to nephron damage and glomerular filtration reduction. The therapy of these conditions implies the application of hemodialysis, peritoneal dialysis, and organ transplantation [9]. Also, chronic liver diseases of different etiologies, permanent damage to the function and numerous consequent complications represent indications for liver transplantation.

Oral changes before transplantation of solid organs

Chronic renal diseases are accompanied by frequent clinical manifestations on other organs and systems, or other chronic diseases, among which poorly controlled diabetes and cardiovascular diseases are the most common. In addition, the adverse effects of numerous drugs and therapies have resulted in a wide spectrum of various oral manifestations in about 90% of patients with renal insufficiency [10]. Chronic liver diseases and permanent damage to the functions of this organ often lead to the occurrence of oral diseases affecting oral mucous membrane and salivary glands, gingiva and periodontal tissues, jaw bone, and hard dental tissue [8].

In patients with renal and hepatic insufficiency, extensive plaque cumulation is observed, as well as the presence of mineralized deposits on the teeth, gingival inflammation, spontaneous bleeding or bleeding after gingival probing, prolonged and increased bleeding after some dental procedures, gingival recession and loss of the adherent epithelium, as well as the presence of periodontal pockets [2, 8, 11]. All this leads to an increased risk of developing caries. Non-cariogenic damage and the loss of hard dental tissues in the form of erosion as a consequence of nausea, esophageal regurgitation and vomiting can be also observed. Caries in the neck of the tooth crown appears in patients with xerostomia. It often occurs in patients who are on hemodialysis and can also occur due to unwanted effects of drugs, loss of bodily fluids, reduced fluid intake, or breathing through the mouth. Long-standing xerostomia favors the formation of caries and inflammation of the gingiva, complicates speech, chewing and swallowing of food, as well as the retention of prosthetics. In these patients, caries complications such as pulp disease with periapical lesions, acute and chronic dentogenic infections, and residual roots of decayed teeth often occur. All these local complications may be the cause of systemic infections [2]. Chronic liver diseases in children who have not completed the process of odontogenesis lead to characteristic greenish endogenous dental staining. Developmental anomalies of the teeth can be diagnosed in the form of a delayed emergence of permanent teeth and hypoplastic structural anomalies of the enamel in children with chronic kidney disease [3, 12].

Patients with renal insufficiency have a characteristic uremic fetor. They complain of metal taste in the mouth and pain caused by the appearance of uremic stomatitis. Uremic stomatitis is manifested in the form of erythematous-membranous changes, ulcerations, hemorrhagic, and hyper-parakeratotic changes of the oral mucosa [13, 14]. The changes are prone to secondary fungal, viral and bacterial infections. Fungal infections of the *Candida albicans* genus are often the cause of opportunistic infections and occur in the form of pseudomembranous, erythematous and atrophic lesions at the oral mucosa. More frequent presence of fungal infections has been identified in patients with diabetic nephropathy [2, 4]. Viral infections in patients with renal insufficiency are most commonly caused by Herpes simplex type 1 virus (HSV1). Poor oral hygiene, decreased secretion and change in pH of the saliva, altered oral microflora composition, reactivation of the virus, as well as the disturbed integrity of oral mucous membranes favor the occurrence of oral bacterial, viral and fungal infections, their dissemination and the appearance of systemic infections in patients with renal and liver insufficiency [15]. In addition to the above-described, other mucosal lesions such as leukoplakia and lichenoid changes are also frequent in these patients. Patients undergoing dialysis program are also on anticoagulant therapy, which increases the risk of enhanced bleeding in the oral cavity. Chronic renal diseases are often accompanied by anemia due to the reduction of erythropoietin synthesis, as well as hemostatic disorders resulting from altered platelet aggregation, which is manifested by spontaneous bleeding or increased and prolonged bleeding after dental interventions, followed by pallor of oral mucosa and the appearance of petechiae and ecchymosis [13].

Metabolic disorders, acidosis, hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism occurring in 92% of hemodialyzed patients lead to the occurrence of renal osteodystrophy. Demineralization, reduction in the number of trabecula and the thickness of the bone cortex are noticed on the jaw bones and temporomandibular joint. On the tooth-supporting apparatus, these disorders lead to the loss of the lamina dura, to the expansion of

the periodontal membrane, and to the large destruction of periodontium, causing pathological teeth mobility and their loss [6, 12, 16].

Oral changes after solid organ transplantation

The occurrence of oral changes in patients after transplantation of solid organs is mainly caused by the adverse effects of various drugs and the presence of infection in the mouth. Patients with transplanted organs are on long-term immunosuppressive therapy that reduces the risk of organ rejection. Immunosuppressants often exhibit adverse effects such as nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension, and enlargement of the gingiva. Gingival enlargement is at the same time the most frequent change in soft tissue of the oral cavity, which, in addition to the effects of immunosuppressive therapy, is also favored by combination of immunosuppressants and some drugs used for reducing blood pressure, as well as extensive dental plaque cumulation. Children and adolescents are particularly prone to these gingival changes [17, 18, 19]. The greatest tendency to gingival enlargement is evidenced immediately after transplantation and after three months. Long-term immunosuppressive therapy, most often after two years, caused appearance of granulomatous changes in the oral mucosa and dorsal surface of the tongue, enlargement of the lips, the appearance of angular cheilitis and fissures on the lips, pigmentation on the oral mucosa and erythroplakia. Patients complain of dry mouth, mouth sores, bad odor from mouth, and bleeding gums during tooth washing [20]. An unusual proliferation of lymphocytes in the post-transplant period leads to lymphoproliferative changes in the paranasal cavities, in the oral cavity, on the larynx and salivary glands [21].

Long-term immunosuppressive therapy, poor oral hygiene and untreated oral diseases can be the cause of numerous infections. In patients on immunosuppressive therapy, even microorganisms that form a normal oral flora can be the cause of common infections. Various bacterial and fungal infections caused by Candida species are commonly seen in patients following kidney transplantation. Also, a greater presence of Herpes simplex virus type 1, Epstein–Barr virus, and Cytomegalovirus was evidenced in sputum in these patients. In addition to the fact that these microorganisms are causes of numerous oral changes and disruption of the integrity of the oral mucous membranes, there is the possibility of their dissemination, onset of systemic infection and the risk of rejection of the transplanted organ [20–24].

The tendency to epithelial dysplasia, occurrence of premalignant and malignant lesions in oral mucosa after organ transplantation, was also observed. The predisposing localization of malignant lesions is the skin of the head and neck as well as mouth and lips, with squamous and basocellular carcinomas being the most common ones. Several factors lead to the emergence of oral cancer, with long-term application of immunosuppressive therapy, inadequate immune response of the organism to the activation of malignant cells, and the presence of papillomas and other oncogenic viruses being most commonly implied [25].

TRANSPLANTATION OF HEMATOPOIETIC STEM CELLS

Transplantation of cells, that is – hematopoietic stem cells, can be allogeneic and autologous. Standard indications for the hematopoietic stem cell transplantation are inborn and acquired diseases of the lymphohematopoietic system and some solid tumors [26, 27].

Oral changes before transplantation of hematopoietic stem cell

In this period, changes in oral tissues arise as part of the adverse effects of very aggressive chemotherapy or combined chemotherapy and radiotherapy, which are applied under various protocols for treatment of the most severe malignancies. The oral cavity is very sensitive to the direct and indirect effects of cytotoxic therapy. Direct stomatotoxicity of cytostatics is a consequence of the non-specific effect of drugs on cells in the process of division, when in the addition to malignant cells, healthy cells are also involved [28, 29]. The tissues with faster cellular cycle are more extensively affected, including oral tissues with a cellular division cycle of 7–14 days. Cytostatic drugs result in the reduction of basal layer regeneration of the oral epithelium and occurrence of mucositis most often a week after the therapy is administered. Buccal mucosa, lips, soft palate, and the ventral side of the tongue, as well as the floor of the oral cavity, are usually affected [30]. According to the World Health Organization criteria for the assessment of toxic effects of cytostatics on oral tissues, mucositis is defined in the range from individual painless ulceration to highly prominent erythema and edema of oral mucosa with multiple, extremely painful ulcerations that require the application of enteral or total parenteral nutrition [26, 31, 32]. Mucositis is more common in young people due to increased mitotic activity of oral epithelial cells in younger age. The intensity of mucositis depends on the type and dose of cytostatics, the length of treatment, the individual sensitivity of the patient, and the condition of the oral cavity before initiation of the therapy [33, 34]. The onset of mucositis is directly related to the degree of neutropenia resulting from the effects of cytostatics on the bone marrow and their indirect stomatotoxic effect. Owing to their myelosuppressive action, cytostatics lead to thrombocytopenia and granulocytopenia. Thrombocytopenia results in the onset of petechiae in the oral mucosa and frequent bleeding in the oral cavity, and granulocytopenia leads to an increased risk of the occurrence of oral infections [35]. Due to changes in the oral mucous membrane and parenchyma of the salivary glands after the application of therapy for hematologic malignancies, as well as stress, in the period prior to the tissue and cell transplantation, reduction in the secretion of stimulated saliva may be observed. Poor oral hygiene and decreased salivary secretion lead to a greater number of diseased teeth and the higher prevalence of periodontal disease [10].

Oral changes after hematopoietic stem cell transplantation

The causes of early complications in the form of febrile neutropenia and mucositis are the application of high-dose chemotherapy or a combination of high-dose chemotherapy and irradiation of the body in the conditioning regimen prior to hematopoietic stem cell transplantation, as well as bone marrow aplasia within the first 3–4 weeks following transplantation [27, 36]. Pain and bleeding, xerostomia due to transient dysfunction of the salivary glands, taste disturbance and hypersensitivity of dentin may appear. Saliva becomes viscous, resulting in reduced lubrication of the oral mucosa. The accumulation of dental plaque is increased, which influences the change in the qualitative and quantitative composition of the oral microflora. Loss of antibodies and other antibacterial proteins, changes in the salivary glycoprotein concentration can compromise the barrier function of oral mucous membranes and increase the risk of developing infections. Poor oral hygiene, untreated caries and caries complications, extensive periodontal disease, and dental infections can be the cause of streptococcal bacteremia in the period immediately following the hematopoietic stem cell transplantation [28, 36, 37].

Allogeneic hematopoietic stem cell transplantation is often accompanied by the onset of graft-versus-host disease. This disease is a multisystemic immune phenomenon that occurs due to the immune response of donor immunocompetent T-lymphocytes and recipient cells, and may have an acute and chronic form. Oral lesions in acute form are most commonly localized in buccal mucosa, mucous membranes of lips, in the tongue, hard and soft palate, and mouth floor in the form of painful, erythematous ulcerations and desquamations. These oral changes may be the initial manifestations of the acute form of the graft-versus-host disease [6, 37, 38]. The chronic form of this disease occurs after 100 days of transplantation of hematopoietic stem cells. It is associated with painful diffuse erythema, lichenoid changes, painful ulcerations, and desquamations of irregular shape, the appearance of papules and mucocele on the oral mucous membrane. Oral mucous atrophy with a feeling of burning and sticking and limited opening of the mouth is also common [39]. Progressive atrophy of the salivary glands leads to xerostomia, dysphagia and dysgeusia, and opportunistic viral, bacterial, and fungal infections can also occur. Numerous oral changes can be followed by multiple systemic changes primarily on the skin, eyes, gastrointestinal tract, and the liver. Oral mucosal lesions are accompanied by erythematous changes in the skin, atrophy of the salivary glands, atrophy of the lacrimal glands, i.e., xerostomia, while limited mouth opening was accompanied by sclerotic changes on the skin. Chronic graft-versus-host disease is in approximately one half of allogenic tissue and cell transplantation the leading cause of non-relapse mortality [38, 40].

In addition to numerous systemic diseases, several years after hematopoietic stem cell transplantation, a greater distribution of oral diseases is observed: gingival inflammation due to the presence of dental plaque, gingival enlargement in patients on immunosuppressive therapy and as a consequence of vascular and fibrotic gingival changes, increased incidence of caries and significantly higher colonization of *Streptococcus mutans* and *Lactobacilli* in saliva compared to healthy population. The occurrence of oral squamous carcinoma is also a late complication of hematopoietic stem cell transplantation. The etiology of these malignancies is not fully understood, but it is thought to be found in long-term immunosuppressive therapy, the presence of oral lesions in chronic graft-versus-host disease, and in the presence of oncogenic viruses [25]. In children subjected to high doses of chemotherapy and radiation therapy during treatment of malignant diseases, more frequent occurrence of developmental dental anomalies is observed several years after the hematopoietic stem cell transplantation. Structural irregularities in the teeth, mineralization disorders of hard dental tissues, irregularities in the length and shape of the teeth roots, reduced tooth crown size, as well as the lack of a smaller or greater number of teeth may occur [35, 40].

CONCLUSION

Oral changes are widely distributed both in the period before and after transplantation of solid organs and hematopoietic stem cells, i.e., numerous systemic diseases are accompanied by pronounced oral manifestations. These changes with frequent local symptoms impair the quality of life of patients, aggravate the underlying disease, as well as the general condition of patients before transplantation and can significantly disturb the course and outcome of the transplant itself. It is therefore necessary to point out the importance and distribution of oral diseases, as well as the measures that have to be taken to reduce the risk of these diseases. Good cooperation is needed between dentists and doctors of other specialties, and adequate dental treatment should be an integral part of the protocol for the treatment of patients at each stage before and after transplantation. The former contributes to the success of the transplant itself, reduces the negative impact of oral diseases on the course and outcome of the underlying disease, and significantly improves the quality of life in the peritransplant period.

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Оралне промене код пацијената пре и после трансплантације солидних органа и матичних ћелија хематопоезе

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САЖЕТАК

Увод/Циљ Циљ овог рада је да се укаже на распрострањеност и тежину оралних обољења код пацијената у периоду пре и после трансплантације солидних органа и матичних ћелија хематопоезе.

Методе Претражена је литература са базама података на *PubMed*-у.

Резултати Развој и унапређење трансплантационе медицине у специјализованим центрима доводи до све већег броја пацијената са трансплантираним солидним органима и матичним ћелијама хематопоезе, како одраслих тако и деце. Код пацијената који су подвргнути процедури трансплантације солидних органа и матичних ћелија хематопоезе се, и поред успешности терапије, могу уочити бројне промене и компликације на другим органима и у фази пре и после трансплантације. Системска обољења и стања везана за трансплантацију органа и ћелија праћена су бројним оралним манифестацијама. Најчешће оралне промене су увећање гингиве, десквамација оралног епитела, веома болне улцерације, полипоидне и грануломатозне промене на оралној слузокожи, обољења тврдих зубних ткива са честим компликацијама, развојне аномалије зуба код деце млађег узраста, а у каснијој фази и појава оралног карцинома. После трансплантације, промене у усној дупљи и другим органима се јављају у зависности од трансплантационог периода у којем се пацијент налази и од примењене имуносупресивне терапије.

Закључак Распрострањене оралне промене пре и после трансплантације солидних органа и матичних ћелија хематопоезе указују на значај правовремене и добре сарадње стоматолога и лекара који лече основно обољење.

Кључне речи: трансплантација органа; трансплантација матичних ћелија хематопоезе; орална обољења

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови**,** наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh)*.

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°*C*), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доле наведене адресе и број телефона.

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The papers are always submitted with Summary in both English and Serbian, included in the manuscript file. The text of the manuscript should be typed in *MS Word* using the *Times New Roman* typeface, and font size 12 pt. The text should be prepared with margins set to 25 mm and onto A4 paper size, with double line spacing, aligned left and the initial lines of all paragraphs indented 10 mm, without hyphenation. Tabs and successive blank spaces are not to be used for text alignment; instead, ruler alignment control tool and *Toolbars* are suggested. In order to start a new page within the document, *Page Break* option should be used instead of consecutive enters. Only one space follows after any punctuation mark. If special signs (symbols) are used in the text, use the *Symbol* font. References cited in the text are numbered with Arabic numerals within parenthesis (for example: [1, 2]), in order of appearance in the text. Pages are numbered consecutively in the right bottom corner, beginning from the title page.

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