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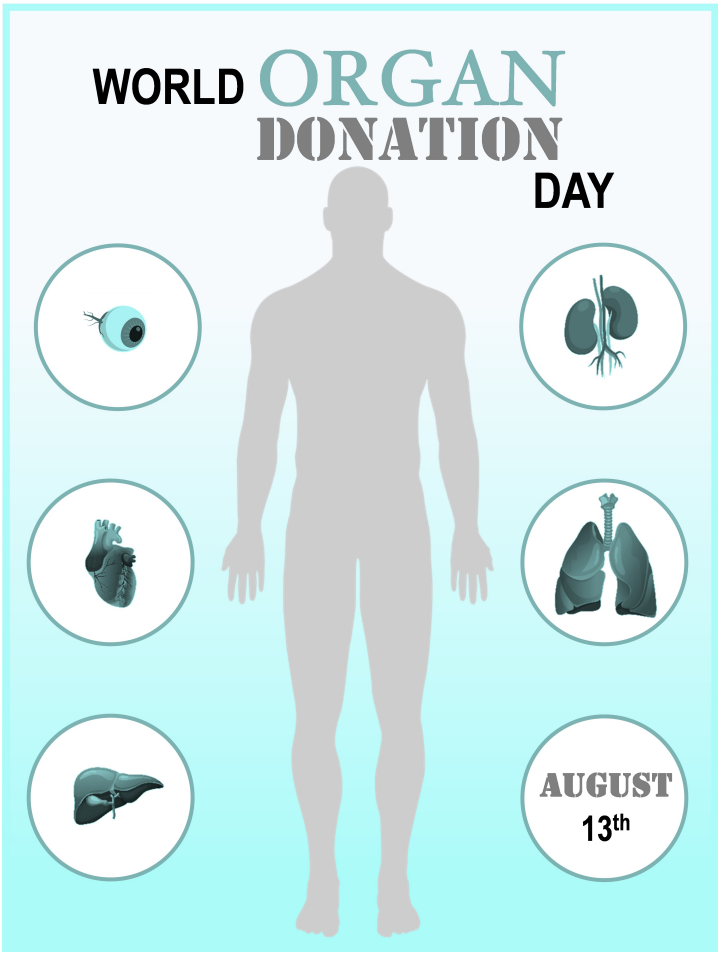

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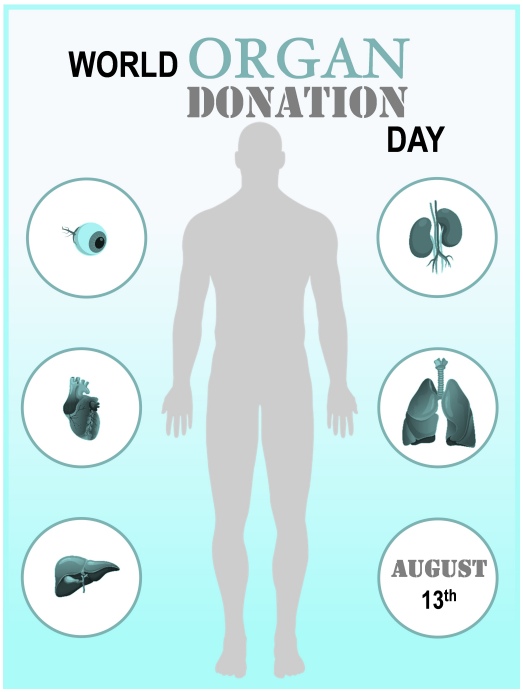

World Organ Donation Day (WODD) was adopted in 2005 by the World Health Organization and the International Society for Organ Donation. Since then, WODD has been observed on August 13 every year as one of the ways of raising collective awareness of the importance of organ donation. It is a day of education about the importance of organ donation but also an opportunity to eliminate the many misconceptions in relation to this act. The theme of WODD 2023 is “Step up to volunteer; need more organ donors to fill the lacunae”. According to the current data from the Ministry of Health of the Republic of Serbia, more than 800 people are waiting for kidney, liver, or heart transplants, and their only hope is “getting a new” organ.

Svetski dan doniranja organa (SDDO) su prvi put obeležile Svetska zdravstvena organizacija i Međunarodno društvo za doniranje organa 2005. godine. Od tada se SDDO obeležava 13. avgusta svake godine kao jedan od načina da se podigne kolektivni nivo svesti o značaju doniranja organa. To je dan edukacije o značaju doniranja organa, ali i prilika da se otklone mnogobrojne zablude koje postoje u vezi sa ovim činom. Tema SDDO 2023. godine je „Postani dobrovoljni davalac; potrebno je više davalaca da se praznina popuni”. Prema trenutnim podacima Ministarstva zdravlja Republike Srbije, u našoj zemlji na transplantaciju bubrega, jetre i srca čeka više od 800 ljudi, za koje je jedini spas „dobijanje novog” organa.

CURRENT TOPIC

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Dentistry 4.0 concept in designing and manufacturing removable partial denture frameworks

Koncept „Stomatologija 4.0“ u planiranju i izradi skeleta parcijalne proteze

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Key words:
computer-aided design; dentistry; denture design; denture, partial, removable.

Ključne reči:
kompjutersko oblikovanje; stomatologija; zubna proteza, oblikovanje; zubna proteza, parcijalna, mobilna.

Introduction

Dentistry and the global concept of digital transformation go together very well. The result is deleting borders between the physical and digital. That deletion of boundaries led to automation and robotization going at the expense of cyber-physical systems (CPS) enabled by the Internet of Things and cloud computing [1–3]. Analogous to the Fourth Industrial Revolution, dentistry conceived in this way is called Dentistry 4.0.

In recent years, Dentistry 4.0 has been the most common topic of many professional meetings. Some authors say that we are in the entrance hall of this global concept, while others, including the authors of this paper, believe that we are well inside it. Thanks to Dentistry 4.0, several diagnostic procedures, as well as laboratory and clinical procedures, have become part of the CPS. There are many areas of dentistry where diagnosis, planning, and therapy are based on highly automated processes and digitalized flows [digital impressions, computer-aided design (CAD) and computer-aided manufacturing (CAM) denture technology, digital radiography and cone-beam computer tomography (CBCT), digital face-bow and virtual articulators, computer-guided implant surgery, and computer-guided diagnostics and treatment in orthodontics, etc.] [1, 2].

In this paper, we described and gave a critical review of the Dentistry 4.0 concept in designing and manufacturing removable partial denture (RPD) frameworks.

RPD frameworks can be made using different techniques. The RPD framework fabricated by casting has a long tradition, and dental appliances obtained using this technique have good clinical results. Cast patterns and frameworks are often used in research to compare results with selective laser melting and sintering frameworks and patterns [4–7]. There are two possibilities for digitalization in manufacturing the RPD framework: the analog-digital and the digital option.

Analog-digital method of RPD frameworks production

The analog-digital method or indirect metal production is a step towards fully implementing the Dentistry 4.0 concept in the design and fabrication of the metal RPD framework. In fact, this method combines analog and digital systems depending on the equipment of dental offices and dental laboratories.

Analog technique (AT) – digital technique (DT) in designing and manufacturing RPD frameworks has the following steps: 1) physical impression with elastic materials – AT; 2) making a master (stone) model – AT and scanning the master model with an extraoral scanner – DT; 3) digital survey and design – DT; 4) print resin framework pattern – DT and investing a printed framework pattern in investment materials – AT; 5) preheating, heating, and casting – AT; 6) sandblasting, surface finishing, and polishing of RPD frameworks – AT.

This technique introduces digitalization elements into the conventional process of creating a metal RPD framework. An RPD framework is designed on a computer using available commercial programs. A virtual RPD design in Standard Tessellation Language format (STL file) is then sent to a 3D printer that prints the RPD framework in a polymer. The print

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ed polymer RPD framework is visually controlled and, after placing sprues, enters the investment material (forming a refractory block) [8]. The following procedure is the same as in the conventional method. The advantages of this combined technique are simplified design (diagnostic survey is performed on a computer) and the facilitated creation of a virtual model of the RPD framework. There is no preparation of the master model for duplication, no duplication of the master model in the investment materials, and no dipping in wax of the refractory model and savings in time and materials.

The disadvantages of this technique include having a computer, a design program, and a 3D printer for polymer materials.

Digital method of RPD frameworks production

The digital method, or direct metal production of RPD frameworks, actually implies the implementation of Dentistry 4.0 at full capacity. The stages of this technique are intraoral digital scanning, digital model creation, digital survey and design, 3D printing and heat treatment, finishing and polishing and printing of the working model.

Intraoral digital scanning

After usual introductory procedures, analysis of the diagnostic cast, and preparation of retention teeth, a digital impression of supporting tissues is taken (Figure 1). Digital impressions, also known as 3D intraoral scanning (IOS) for RPD are indicated for Kennedy Class III and Class IV partially edentulous arches (bounded saddles) with several missing teeth [9–11]. It is necessary to take several scans of both arches. The ultimate result of scanning software processing is a full-mouth image. Caution is required at the free-end saddles (Kennedy Class I and Class II). Free saddle boundaries on the digital impression are equal to the free saddle boundaries taken by the mucostatic impression. The protocol states that the free saddle should be impressed within its functional boundaries, in other words, by the mucodynamic impression. In exceptional cases, a digital impression can be taken with a short free saddle and a saddle with low mucosal resilience [12]. In all other cases of the free saddle, a functional impression is desirable. After taking a full-mouth image, a therapist can send the digital impression to a lab online.

Fig. 1 – Taking a digital impression by using a wand-like tool connected to a computer.

Digital model creation

Using a computer and advanced commercial software, a dental technician created a virtual model (Figure 2).

Fig. 2 – Digital model creation – the first step in designing and manufacturing removable partial denture frameworks.

Digital survey and design

RPD frameworks are digitally designed using specialized software through a series of digital steps similar to conventional laboratory procedures. The second step involves determining the path of RPD insertion using commercially available RPD CAD software (Figure 3). The software measures the depth of undercuts and the parallelism of guide surfaces of abutment teeth. The software rotates the virtual model in all three planes and suggests a survey line based on these calculations [13]. The digital model is then oriented for the appropriate path of insertion. The next step includes the blockout of the undercuts and the preparation of the space for the retentive clasp tips (Figure 4). The workflow in the digital design framework of RPD includes laying thin layers of virtual wax and meshwork patterns on the edentulous area, the virtual building of major and minor connectors (Figure 5), and the virtual building of rests and clasp arms (Figures 6 and 7). Before laser melting and sintering a Cobalt-Chromium (Co-Cr) alloy, it is necessary to set up special supports that will be strong enough to hold and stabilize the framework when sintering the alloy (Figure 8). It is often necessary to add cross-arch supporting bars that will connect the left and right sides of the framework and thus further stabilize the object during sintering.

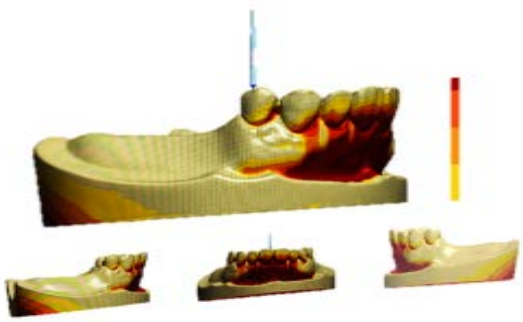

Fig. 3 – The second step in designing and manufacturing removable partial denture frameworks is determining the path of insertion.

Fig. 4 – Virtual blockout of undercuts (pink color) using available removable partial denture computer-aided design software.

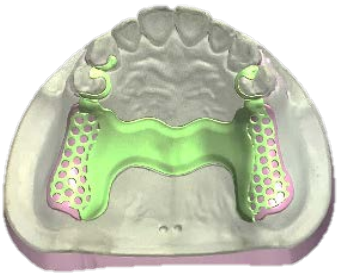

Fig. 5 – Thin layers of virtual wax and meshwork patterns on the edentulous area and the virtual building of major and minor connectors, rests, and bracing parts of the clasp.

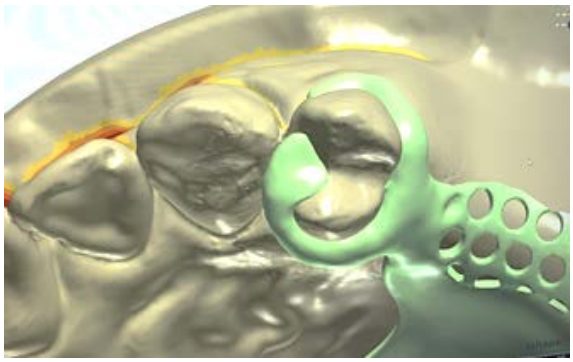

Fig. 6 – Virtual building of the clasp assembly.

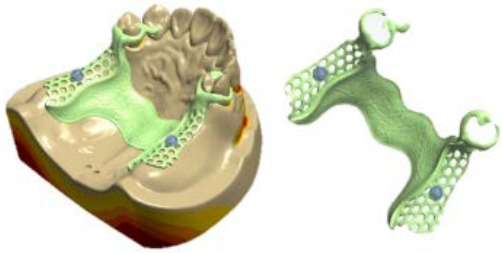

Fig. 7 – Complete adjustment of the framework with connectors, clasps, rests, finish lines, and tissue stops.

Fig. 8 – Illustration of the supports necessary for successfully laser melting and sintering the removable partial denture framework.

Fig. 9 – Moment of laser melting and sintering the cobalt-chromium alloy.

3D printing and heat treatment

From the computer, a digital framework (STL file) is sent to a 3D printer that laser melts and sinters the Co-Cr alloy, building a metal RPD framework. The parameters of the 3D printer are set as default and the dental technician "schedules" the digital frameworks and adjusts their angle to the printer platform. The sintering process takes about 90 min (Figure 9). After the end of sintering, the RPD framework is thermally processed, together with the platform of the 3D machine, in order to release internal stresses.

Finishing and polishing

New DryLyte technology combines at the same time the sandblasting and the mechanical and dry electropolishing of RPD frameworks. Three metal frameworks can be finished/polished simultaneously (about 60 min), which contributes to environmentally friendly technology and time savings (Figure 10).

Printing of the working model and transferring of the RPD framework to the dental office

The digital model (STL file), already used for designing the RPD framework, is sent to a 3D printer (based on the principles of stereolithography) which prints the model in an advanced photopolymer. Now, for the first time, we see the physical working model to which the completed RPD framework is adapted (Figure 11). The RPD framework on the working model is sent to the dental office for further clinical procedures. A finished RPD framework is checked in the

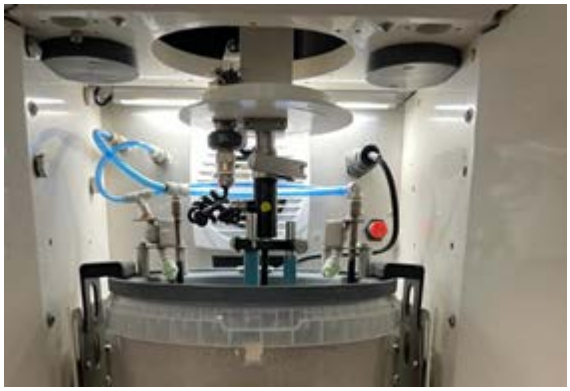

Fig. 10 – Processing of printed metal removable partial denture frameworks by DryLyte technology.

Fig. 11 – A finished removable partial denture framework on the printed model ready to be sent to the dental office.

patient's mouth for fit, retention, and occlusion. The remaining procedure is the same as with conventional methods of making RPDs.

Advantages and disadvantages of the digital concept in designing and manufacturing RPD frameworks

The advantages of the digital concept in designing and manufacturing RPD frameworks are the following: communication between the dentist and the dental technician is simplified; digital impressions, compared to traditional tray-and-putty dental impressions, are much more pleasant for the patient and more comfortable for the therapist; a digital impression, in addition to its accuracy, provides the dentist with the opportunity to have a complete insight into the impression from different angles, allowing them to correct any mistakes immediately while the patient is still in the chair; digital impressions can be sent to the dental laboratory without delay; working time in the laboratory is significantly reduced – there is no preparation of models for duplication and duplication of models in investment materials, no modeling in wax, no placing the sprues, preheating, or casting; *post*-fabrication process of the RPD framework (finishing and mechanical and dry electropolishing) is significantly shortened and facilitated by DryLyte technology; all clinical and laboratory procedures in the manufacturing of RPD frameworks are environmentally friendly; in the long-term estimates, the costs of manufacturing a metal RPD framework have been reduced.

The disadvantages of the digital concept in designing and manufacturing RPD frameworks are negligible compared to the advantages and include the following: the initial costs of an intraoral camera and scanning software; initial costs of 3D printers and the CAD software; increased costs for the education and training of dental technicians; the impossibility of making some special framework shapes of RPD due to limitations of the available software and manufacturing procedures.

Full implementation of the holistic Dentistry 4.0 approach in therapy of the partially edentulous patients with RPD is still not possible. A big step towards achieving this goal has been made with the introduction of the digital concept in designing and building RPD frameworks. The most crucial step in the procedures for fabricating RPD frameworks is to provide as much accuracy as possible in the reproduction of the supporting tissue. Digital impression techniques are recommended for partially edentulous patients with tooth bounded saddles, and the procedure is the same as digital impressions for fixed prosthetics. The accuracy of the digital impression in these cases is excellent, and its indication is unquestionable. Digital impression for free-end saddles is possible with a lot of limitations. Based on the research of many clinicians [14–17], as well as our experience, the traditional silicone impression is recommended in partially edentulous patients with free-end saddles. The silicone impression is poured out in super-hard stone. The stone (master) model is then scanned to obtain a digital model. These are actually the first and second steps of the analog-digital method of RPD framework production. The further procedure is completely digitized. It is possible to do a 3D scan directly from the silicone impression. In that case, it is necessary to print the working model in the polymer on which the framework is adapted and send it to the dental office for further procedure.

The Dentistry 4.0 approach requires the involvement of people of different professions and the knowledge of new-generation dental materials, new technologies, and application possibilities of CPS in dentistry. Materials used today in printing the RPD metal framework are highly sophisticated materials [14, 18–20]. Today, the most precise metal framework RPDs are obtained using special Co-Cr alloys "type 5" according to ISO 22674 (e.g., EOS Cobalt-Chrome RPD, Krailling, Germany; Mediloy S-Co, BEGO, Bremen, Germany).

Thanks to the new technologies (3D printing, DryLyte technology, and other technological innovations) supported by CPS, the degree of automation in the fabrication of metal RPD frameworks today is pretty high.

According to the literature, the accuracy of RPD frameworks fabricated using digital techniques (IOS and Additive Manufacturing techniques) is equal to or better than that of conventional RPD frameworks manufactured in a traditional way [21–25]. Fabricating RPD frameworks using digital design and 3D printing technology is a big step toward creating a smart manufacturing ecosystem in dentistry [15].

The majority of authors believe that, in the future, the expected benefits of this concept in the development of metal RPD frameworks should include high-strength materials with outstanding biocompatibility, excellent precision of fit, and cost-effective dental appliances for dentists and patients [1, 14, 15, 26].

Conclusion

Dentistry 4.0 has changed the face of dentistry over the past decade. The Dentistry 4.0 concept has improved the designing and manufacturing of RPD frameworks in terms of reducing the number of clinical appointments, shorter chair time, and greatly simplifying laboratory procedures. The precise fit of the RPD framework on the supporting tissues, comfort in work for both the dentist and the patient, and the absence of medical waste are a big step forward in the dental profession.

Conflict of interest

The authors declare no conflict of interest.

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Retrospective analysis of hospitalization rates in patients with schizophrenia 12 months before and 12 months after the switch to once-monthly long-acting injectable paliperidone palmitate

Retrospektivna analiza stope hospitalizacija bolesnika sa shizofrenijom 12 meseci pre i 12 meseci posle uključivanja jednomesečnog dugodelujućeg injekcionog paliperidon palmitata

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Abstract

Background/Aim. There is no available published data about the use of long-acting injectable paliperidone palmitate (PP) in schizophrenia patients in the Republic of Serbia. The aim of this study was to assess hospitalization rates before and after the switch to once-monthly long-acting injectable PP in schizophrenia patients, as well as their compliance with this drug. **Methods.** We conducted a retrospective cross-sectional study in which hospitalization rates were evaluated 12 months before and 12 months after the switch to once-monthly long-acting injectable PP in 113 schizophrenia patients. The age of the enrolled patients was between 18 and 66 years. **Results.** The average age of the enrolled patients was 38.36 ± 11.62 years. Among them, 77 (68.1%) were male, and 36 (31.9%) were female. Out of the total number of 113 patients treated with once-monthly injectable PP, 78 (69.03%) were on monotherapy, while 35 (30.97%) had one additional oral antipsychotic (risperidone, olanzapine, aripiprazole, or clozapine). Out of the total number of 113 patients, 68 (60.18%) were not hospitalized in the 12-month period before the switch to once-monthly long-acting injectable PP, while 45 (39.82%) were hospitalized in the same period. Given that 8 patients out of the total number of 113 were excluded from therapy due to an adverse event or their own decision in the period after the switch to PP, the analysis of the hospitalization rate after the switch to PP was performed for the remaining 105 patients, of which 9 (8.57%) were hospitalized in the period after the switch to PP, and 96 (91.43%) were not. **Conclusion.** Our results show high compliance in the treatment with once-monthly injectable PP and a positive impact of treatment with this drug on low hospitalization rate in a 12-month period in patients with schizophrenia. Considering the availability of this drug in the Republic of Serbia, these results encourage the use of once-monthly injectable PP as an important therapeutic option in schizophrenia patients.

Key words:
antipsychotic agents; delayed-action preparations; drug-related adverse effect and adverse reactions; hospitalization; paliperidone palmitate; patient compliance; schizofrenia; serbia.

Apstrakt

Uvod/Cilj. Do sada nije bilo dostupnih publikovanih rezultata o upotrebi dugodelujućeg preparata paliperidon palmitata (PP) kod bolesnika sa shizofrenijom, lečenih u svakodnevnoj kliničkoj praksi u Republici Srbiji. Cilj rada bio je da se ispita stopa hospitalizacije bolesnika sa shizofrenijom pre i nakon uključivanja jednomesečnog dugodelujućeg injekcionog PP, kao i komplijantnost bolesnika lečenih tim lekom. **Metode.** Retrospektivnom studijom preseka ispitivana je stopa hospitalizacije kod 113 bolesnika sa dijagnozom shizofrenije, u periodu od 12 meseci pre uključivanja jednomesečnog dugodelujućeg injekcionog PP i 12 meseci nakon toga. U studiju su bili uključeni bolesnici starosti od 18 do 66 godina. **Rezultati.** Prosečna starost ispitanih bolesnika bila je 38,36 ± 11,62 godina. Među njima je 77 (68,1%) bilo muškog pola, a 36 (31,9%) ženskog pola. Od 113 bolesnika kojima je uključen PP, 78 (69,03%) bolesnika bilo je na monoterapiji, dok je 35 (30,97%) imalo dodatnu terapiju jednim oralnim antipsihotikom (risperidon, olanzapin, aripiprazol ili klozapin). Od ukupno 113 bolesnika, njih 68 (60,18%) nije bilo hospitalizovano, dok je 45 (39,82%) bolesnika bilo hospitalizovano u periodu od 12 meseci pre uključivanja jednomesečnog dugodelujućeg injekcionog PP. S obzirom na to da je od ukupno 113 bolesnika 8 isključeno sa terapije usled neželjenog događaja

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ili sopstvene odluke u periodu nakon uključivanja PP, analiza stope hospitalizacije posle uključivanja PP izvršena je u grupi od 105 bolesnika, od kojih je njih 9 (8,57%) bilo hospitalizovano u periodu posle uključivanja PP, a 96 (91,43%) nije. **Zaključak.** Naši rezultati pokazuju visoku komplijantnost bolesnika u lečenju jednomesečnim injekcionim PP i pozitivan uticaj tog leka na nisku stopu hospitalizacije bolesnika sa shizofrenijom, tokom perioda praćenja od 12 meseci. S obzirom na dostupnost PP u Republici Srbiji, ovakvi rezultati su ohrabrenje za njegovu upotrebu, kao važne terapijske opcije za lečenje bolesnika sa shizofrenijom.

Ključne reči:
antipsihotici; lekovi, produženo dejstvo; lekovi, neželjena dejstva i neželjene reakcije; hospitalizacija; paliperidon palmitat; bolesnik, saradnja; shizofrenija; srbija.

Introduction

Schizophrenia and schizophrenia spectrum disorders are chronic and debilitating disorders, frequently associated with significant and long-term negative impacts on the capability of the affected individuals to function in all aspects of living [1]. Antipsychotic medications are the backbone of treatment both for the acute phase and the maintenance treatment of these patients. Newer generation oral antipsychotic medications are recommended as the first line treatment of patients with schizophrenia both by local and international guidelines [2, 3]. Current recommendations for the long-term treatment of schizophrenia patients with antipsychotic medications are based on studies showing lower rates of relapses with continuous treatment compared to alternative strategies like discontinuation or intermittent treatment [4]. The most frequently used criteria in studies for the definition of relapse was reemergence or deterioration of disease symptoms after achieving remission and before the recovery, as well as the need for hospitalization due to psychiatric reasons. Relapse in schizophrenia has a negative impact on patient functioning and quality of life, leading to worse treatment outcomes, therapeutic resistance, prolonged periods of recovery, and decreased probability of achieving remission [5]. Besides that, relapse, including more frequent hospitalizations, significantly affects the costs of treatment for schizophrenia patients [6]. Since one of the characteristics of schizophrenia is the lack of insight, that is, the patients are unaware of their illness and its consequences, this frequently leads to challenges in long-term treatment compliance [7]. Long-acting antipsychotic medications are developed in order to improve treatment compliance and eliminate the need for every day dosing regimens [8]. Up-to-date, long-acting formulations were developed for fluphenazine, haloperidol, flupentixol, zuclopenthixol, risperidone, aripiprazole, olanzapine, and paliperidone, while long-acting formulations of fluphenazine, haloperidol, risperidone, and paliperidone are approved for use in the Republic of Serbia (RS) and reimbursed by National Health Insurance Fund [9–11].

Long-acting antipsychotic medications demonstrated plenty of advantages, like simplicity of use, following of treatment compliance, regular contact with patients, lower risk of accidental or deliberate overdose, and better correlation of dose and plasma concentration. However, some disadvantages occurred as well, like slow dose titration, longer time to establish plasma steady state, local adverse effects, or long-term adverse effects [12]. Long-acting injectable antipsychotic medications proved their efficacy by ensuring stable plasma concentrations of the drug over a few weeks period [13], decreasing the risk for treatment failure [14].

Long-acting injectable paliperidone palmitate (PP) is approved for use in the RS as a once-monthly intramuscular injection in doses of 50 mg, 75 mg, 100 mg, and 150 mg with the indication for use in adult patients with schizophrenia whose disease was stabilized with the use of risperidone or paliperidone. In some adult schizophrenia patients who previously had the response on oral paliperidone or risperidone, whose psychotic symptoms are mild or moderate, long-acting injectable PP can be used without previous stabilization with oral therapy. Besides that, PP is approved in the RS as a three-month long-acting injectable formulation in the doses of 175 mg, 263 mg, 350 mg, and 525 mg for treating adult schizophrenia patients previously stabilized with once-month long-acting injectable PP. Paliperidone exerts its pharmacological actions by binding to serotonin 5-HT2 and dopamine D2 receptors and, to a lower extent, blocks H1 histaminic and alpha-2 adrenergic receptors. Paliperidone does not bind to cholinergic receptors. The efficacy of paliperidone is demonstrated in pivotal registration studies where it showed efficacy in the acute treatment of schizophrenia, maintenance symptom control treatment, as well as in the prevention of recidivism. The safety profile of paliperidone consists of the expected adverse effects profile for the described pharmacodynamic actions – extrapyramidal syndrome, sedation/somnolence, hyperprolactinemia, increase of body weight, as well as class dependant cardiovascular adverse effects [9].

To our knowledge, there is no up-to-date published real-world evidence about the use of long-acting injectable PP in schizophrenia patients in the RS. The aim of this study was to evaluate hospitalization rates and compliance rates before and after the switch to once-monthly long-acting injectable PP in schizophrenia patients.

Methods

This is a retrospective observational cross-section study that evaluates hospitalization rates in the period of 12 months before and 12 months after the switch to once-monthly long-acting injectable PP in schizophrenia patients. This study enrolled schizophrenia patients who were administered treatment with once-monthly long-acting injectable PP in one tertiary mental health center from October 2017 to September 2019. The study was approved by the Ethics Committee of

the Clinic for Mental Disorders "Dr. Laza Lazarević", Belgrade, Serbia (No. 3096, from March 23, 2021). Retrospective data chart review and extraction were performed for the patients who met the abovementioned inclusion criteria, and the following data were collected: demographic characteristics, data about treatment duration, administered therapy, discontinuation of therapy, and data about hospitalizations. Using the method of the defined daily dose of antipsychotic medication [15], oral antipsychotic medication doses were calculated and expressed as olanzapine equivalent. The enrolled patients were 18 to 66 years old and the analysis did not include patients who did not have complete data for the follow-up period of 24 months.

Statistical analysis

Statistical analysis was performed using the statistical program SPSS (SPSS for Windows, release 24.0, SPSS, Chicago, IL). Descriptive statistics methods were used for the analysis. Numerical variables were presented as mean ± standard deviation (SD) and median with interquartile range (25^{th}–75^{th} percentile). Categorical data were presented as numbers and percentages.

Results

Sociodemographic characteristics and disease history

Considering described inclusion criteria, the study enrolled 113 patients with the diagnosis of schizophrenia who were administered treatment with once-monthly long-acting injectable PP. Regarding the demographic patient characteristics at the moment of administration of PP, it was found that the mean age of enrolled patients was 38.36 ± 11.62 years. Among them, 77 (68.18%) were male, and 36 (31.9%) were female. The median duration of overall disease treatment until the moment of administration of PP in the therapy was 72 months (range 12–348).

Treatment characterization

From the total number of 113 patients, 52 (46.0%) were switched from other long-acting antipsychotic medication (haloperidol, risperidone) to long-acting PP, while 61 (53.9%) of them were switched from oral antipsychotic medication to long-acting PP. The median dose of administered PP was 100 mg (range 75–150 mg). PP monotherapy was observed in 78 (69.03%) patients, while 35 (30.97%) had one additional oral antipsychotic (risperidone, olanzapine, aripiprazole, or clozapine). The median dose of additional oral antipsychotic medication expressed as olanzapine equivalent was 4.85 mg (range 2.81–7.38 mg).

Treatment outcomes

From the total of 113 patients who were switched to treatment with PP, 6 (5.3%) patients discontinued treatment by their own decision (without available reason for discontinuation), 2 (1.8%) discontinued treatment due to adverse effects (sedation n = 1, malignancy n = 1), and the total number of patients who continued the treatment was 105. Out of those 105 patients, 9 required hospitalization due to disease exacerbation. From the total number of 113 patients, 68 (60.2%) did not have hospitalization in the period of 12 months before the switch to once-monthly long-acting injectable PP, while 45 (39.82%) patients had hospitalization in the same period. In the analysis of the hospitalization rate after the switch to once-monthly PP, 105 patients (who were not discontinued from treatment due to an adverse event or their own decision) were included. Given that out of the total number of 113 patients, 8 were excluded from therapy due to an adverse event or their own decision in the period after the switch to PP, the analysis of the hospitalization rate after the switch to PP was performed for the remaining 105 patients, and the results showed that 9 (8.57%) of them were hospitalized in the period of 12 months after the switch, while 96 (91.43%) were not hospitalized in the same period.

Discussion

This retrospective study evaluating hospitalization rates before and after the switch to once-monthly long-acting injectable PP showed a lower percentage of hospitalizations in the same group of schizophrenia patients after the switch to PP in the follow-up period of 12 months than in the period of 12 months before the switch. Considering the limitations of this study (retrospective observational design; patients with missing data were not enrolled; heterogeneity of administered antipsychotic medication before the switch to PP; insufficient sample size for comparison regarding type, formulation, and dose of previously administered antipsychotics), no definite conclusions about the reduction of hospitalization risk in schizophrenia patients treated with once-monthly PP can be drawn based on our results. However, our results can give important insights into the treatment of schizophrenia patients with once-monthly injectable PP. The result showing that 91.43% of patients treated with once-monthly PP did not have hospitalization in the period of 12 months represents a very positive signal regarding an important outcome in schizophrenia treatment such as hospitalization, and not only the treatment outcome but also the outcome of resource utilization that hospitalization imposes. Interpretation of our results must take into consideration one important finding – 30.97% of patients had one additional oral antipsychotic medication, which prevents ascribing the result of the high percentage of patients who did not have hospitalization in the 12-month period due to the effects of PP alone. Besides that, based only on the high percentage of patients treated with PP who did not have hospitalization in the period of 12 months, we cannot draw conclusions regarding the quality of the remission, symptom severity, and functional outcomes since these parameters were not evaluated; however, the result can only be interpreted as a surrogate parameter of effectiveness.

One study [16] conducted on a larger sample (n = 2,275) of patients with schizophrenia compared hospitalization rates of patients treated with three-month injectable PP, one-

month injectable PP, long-acting injectable aripiprazole, and oral antipsychotics showed that the best rate was observed in the group of patients receiving three-month injectable PP where in the period of 12 months, 92% of patients did not have psychiatric hospitalization, while for the same period of time, the exact result for once-monthly PP was not reported, but the presented Kaplan-Meier curve showed that the value was slightly below 80%. In the same study, during the period of 18 months, 72.1% of patients with schizophrenia treated with once-monthly injectable PP were not hospitalized. Another study [17], conducted on a smaller sample (n = 51) which evaluated hospitalization rates of patients with schizophrenia treated with once-monthly PP, showed that in the period of 12 months, only 9.8% of patients had psychiatric hospitalization, which is in line with our results. The same study showed that 74% of patients during the period of 12 months, besides once-monthly injectable PP, had additional oral antipsychotic therapy, which is considerably higher than our results of 30.97%. One study showed that during the period of 12 months in 188 analyzed schizophrenia patients treated with once-monthly PP median of hospitalizations was 0 (range 0–4) [18]. While our study did not evaluate the presence, frequency, and type of adverse events of treatment with once-monthly PP, results regarding the discontinuation of treatment were very encouraging. Firstly, the result that only 6 (5.3%) out of 113 patients decided to discontinue the once-monthly PP treatment on their own (without evidence of the reason for that decision), and that only 2 (1.8%) patients discontinued due to an adverse event, can indicate good tolerability of this drug and its positive effects on treatment compliance. These results are identical to previous studies, which found low discontinuation rates for once-monthly PP [16, 18, 19].

Conclusion

Our results show high compliance in the treatment of schizophrenia patients with once-monthly injectable PP, as well as the positive impact of this drug on low hospitalization rates in these patients over the period of 12 months. Considering the availability of this drug in the RS, these results encourage its use as an important treatment option for schizophrenia patients. Further studies generating real-world evidence of once-monthly PP use should be based on larger samples from multiple centers and longer follow-up periods, make comparisons based on type, formulation, and dose of previously used antipsychotic medications, the impact of this drug on disease symptoms, functional outcomes, and lastly, but maybe most important, patient-reported outcomes.

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Analgesic effect of pericapsular nerve group block on elderly patients undergoing hip replacement

Analgetski efekat blokade grupe perikapsularnih nerava kod starijih osoba koje su podvrgnute zameni kuka

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Abstract

Background/Aim. Pericapsular nerve group block (PNGB) does not affect the motor nerve while blocking the obturator and femoral nerves. The aim of the study was to determine the application value of PNGB for hip replacement in the elderly. **Methods.** Ninety elderly patients who underwent hip replacement from March 2019 to October 2020 were randomly divided into the fascia iliaca compartment block (FICB) group and the PNGB group. FICB and PNGB were performed prior to subarachnoid block (SAB). Their baseline data, operation conditions, incidence of adverse reactions, visual analog scale (VAS) score, heart rate (HR), mean arterial pressure (MAP), plasma cortisol (COR), and epinephrine (E) levels were compared. **Results.** VAS score, E, and plasma COR levels in the PNGB group were lower than those in the FICB group at time points T_2–T_4 (T_2: 10 min after nerve block; T_3: at position changing; T_4: after position changing) ($p < 0.001$). There were no significant differences in HR and MAP between the two groups at any time point ($p > 0.05$). In the PNGB group, the ultrasonic imaging time was shorter, the time point of pressing patient-controlled analgesia (PCA) for the first time was later, and the numbers of pressing PCA were fewer than those of the FICB group ($p < 0.001$). No local anesthetic poisoning took place after the nerve block, and no hematoma at the puncture site, nerve injury, nausea and vomiting, dizziness, or delirium occurred. **Conclusion.** Both FICB and PNGB prior to SAB were highly safe for hip replacement in the elderly; however, PNGB has shorter ultrasonic imaging time, better analgesic effect, and milder oxidative stress, so it is worth applying it clinically.

Key words:
aged; analgesia; anesthesia, conduction; arthroplasty, replacement, hip; methods.

Apstrakt

Uvod/Cilj. Blokada grupe perikapsularnih nerava (BGPN) ne utiče na motorni nerv a blokira opturatorne i femoralne nerve. Cilj rada bio je da se utvrdi vrednost primene BGPN tokom zamene kuka kod starijih osoba. **Metode**. Ukupno 90 starijih osoba, podvrgnutih zameni kuka od marta 2019. do oktobra 2020, nasumično su podeljene u grupu bolesnika kojima je izvršena blokada odeljka ilijačne fascije (BOIF) i grupu onih kojima je izvršena BGPN. BOIF i BGPN izvedene su pre subarahnoidnog bloka (SAB). Upoređivani su osnovni podaci bolesnika, uslovi operacije, incidenca neželjenih reakcija, skor na vizuelnoj analognoj skali (VAS), brzina otkucaja srca (BOS), srednji arterijski pritisak (SAP), nivoi kortizola u plazmi (KOP) i epinefrina (E). **Rezultati.** Skor VAS, nivoi E i KOP bili su niži kod bolesnika u grupi BGPN nego u grupi BOIF, u vremenskim terminima T_2–T_4 (T_2: 10 min posle bloka nerva; T_3: pri promeni položaja; T_4: posle promene položaja) ($p < 0,001$). Nije bilo značajnih razlika u vrednostima BOS i SAP između dve grupe ispitanika ni u jednoj od vremenskih tačaka ($p > 0,05$). U grupi BGPN, vreme ultrazvučnog snimanja bilo je kraće, moment u kome je prvi put korišćena analgezije koju kontroliše bolesnik (*patient controlled analgesia* – PCA) se desio kasnije, a broj korišćenja PCA bio je manji u poređenju sa grupom BOIF ($p < 0,001$). Nakon blokade nerva nije došlo do toksičnog efekta lokalne anestezije, ni do stvaranja hematoma na mestu uboda, povrede nerva, mučnine i povraćanja, vrtoglavice i delirijuma. **Zaključak.** I BOIF i BGPN primenjeni pre SAB-a bili su veoma bezbedni tokom procesa zamene kuka kod starijih osoba, ali BPGN ima kraće vreme ultrazvučnog snimanja, bolji analgetički efekat i blaži oksidativni stres, stoga ga vredi primeniti klinički.

Ključne reči:
stare osobe; analgezija; anestezija, provodna; kuk, artroplastika; metode.

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Introduction

Severe pain occurs following hip fractures, especially during early repositioning and examinations [1]. Therefore, minimizing this pain is of great significance for improving patients' comfort and reducing their morbidity and mortality rates. For these patients, oral administration or intravenous infusion of nonsteroidal analgesics is often performed during preoperative hospitalization, which increases the incidence rate of adverse reactions such as dizziness and nausea [2]. In severe cases, some patients may suffer from gastrointestinal bleeding and renal function impairment.

Intraspinal anesthesia is a preferred anesthesia method recommended in the Guidelines on Anesthesia and Perioperative Management of Elderly Hip Fracture Patients in China in the case of no contraindications [3]. However, when the patient is placed in a lateral position before a spinal puncture, the pain can be aggravating, thus increasing cardiovascular risk. Therefore, fascia iliaca compartment block (FICB) can be performed on the affected side before positioning the patient. It was later found in clinical practice that FICB has insufficient analgesia on the medial hip joint due to insufficiency of obturator nerve block, resulting in pain during position changing [4, 5]. Pericapsular nerve group block (PNGB) does not affect the motor nerve while blocking the obturator nerve and femoral nerve [6, 7]. Currently, there are few reports on the application value of PNGB combined with subarachnoid block (SAB) in the elderly with hip replacement.

In this study, the analgesic effect and safety of FICB and PNGB were compared among elderly patients undergoing hip replacement, aiming to provide a basis for clinical application.

Methods

Subjects

This prospective study included a total of 90 elderly patients undergoing a hip replacement in Puren Hospital (Wuhan, China) from March 2019 to October 2020. All included patients were selected and divided into the FICB group (n = 45) and PNGB group (n = 45) using a random number table. Inclusion criteria were as follows: 1) patients aged 65–85 years; 2) patients undergoing unilateral hip replacement for the first time; 3) patients with an American Society of Anesthesiologists (ASA) standard classification of I–II; 4) patients with a preoperative mini-mental state examination (MMSE) score above 24 points; 5) patients with complete clinical medical records; 6) patients with preoperative pain; 7) patients who voluntarily participated and whose families were informed. Exclusion criteria were as follows: 1) patients with coagulation dysfunction or other blood system diseases; 2) patients with severe organ dysfunction, tumor, or serious systemic infectious diseases difficult to be controlled; 3) patients with mental or neurological diseases, communication disorders, cognitive or sleep disorders; 4) patients with a history of chronic pain or long-term use of opioids; 5) patients with poor control of chronic diseases; 6) patients allergic to the drugs used in this study; 7) patients unable to tolerate anesthesia or surgery due to other reasons. This study was reviewed and approved by the Medical Ethics Committee of Puren Hospital (approval No. 20190211004, from March 4, 2019).

Anesthesia methods

Before the operation, all patients were deprived of food and water according to the hospital protocol, and no medication was given. After the patient entered the operating room, the changes in vital signs were routinely monitored by electrocardiography, and peripheral venous access was made. The ultrasound-guided nerve block and subarachnoid anesthesia were performed by the same experienced anesthesiologist.

In the FICB group, while in a supine position, the patient was routinely draped. A line was made between the anterior superior iliac spine and the pubic tubercle, and 2 cm away from the mid-lateral, one-third of the line was selected as the puncture point and disinfected. The 5–13 MHz high-frequency linear array probe covered with a sterile lens jacket and placed parallel to and below the inguinal ligament was used to identify the femoral artery and iliac muscle, and then it was moved outward to the mid-lateral inguinal ligament. After the fascia iliaca image was observed, a bevel-shaped puncture needle (type D, 22 G, 0.71 mm × 80.00 mm) was inserted at an angle of 30–50° and 1 cm above the inguinal ligament, and the needle tip reached the upper iliopsoas in the fascia iliaca compartment through the in-plane puncture technique. Then, 30 mL of 0.25% ropivacaine (Qingyuan Jiabo Pharmaceutical Co., Ltd., China, 2019) was slowly injected after no blood and gas were withdrawn.

In the PNGB group, the patient was routinely draped and disinfected around the puncture point in a supine position. The 5–13 MHz low-frequency convex array probe covered with a sterile lens jacket and placed parallel to the inguinal ligament and slightly above the femoral head was used to identify the iliac crest eminence, anterior inferior spine, pectineal muscle, femoral artery, iliopsoas muscle and its tendons. Then a bevel-shaped puncture needle (type D, 22 G, 0.71 mm × 120.00 mm) was inserted from the lateral to the medial side of the skin 1 cm outside the long axis of the ultrasonic probe; the needle tip was guided onto the musculofascial plane between the posterior pubic branch and the rear of psoas major tendon through the in-plane puncture technique. Then, 30 mL of 0.25% ropivacaine was slowly injected after no blood and gas were withdrawn. During puncture, the movement of the puncture needle should be noticed to avoid damage to the organs. In addition, to avoid local anesthetic poisoning, the presence of blood return should be repeatedly observed during injection.

At 15 min after the block, 2% lidocaine (Jumpcan Pharmaceutical Group Co., Ltd., China, 2019) was used for local infiltration at the optimal space below L_2 in a lateral position with the affected limb upward, and 2.5–3.0 mL of hypobaric local anesthetic solution (2 mL of sterile water for injection containing 1 mL of 1% ropivacaine, self-prepared) was injected into the subarachnoid space. After the operation, patient-controlled analgesia (PCA) was applied to all patients: 10 mg of tropisetron (Beijing Wellso Pharmaceutical Co., Ltd., China, 2019) and 100 μg of sufentanil (Yichang Renfu Pharmaceutical Industry, China, 2019) were diluted with normal sa-

line to 100 mL, the background infusion rate was 2 mL/h, and the patient-controlled dose was 2 mL/time. PCA was locked for 15 min and withdrawn after 48 hrs.

Surgical method of hip replacement

Articular Surface Replacement XL (ASRTMXL) large-diameter metal-to-metal total hip replacement prosthesis (DePuy, Warsaw, USA, 2018) was used. The diameter of the femoral head was 39–63 mm, and the acetabulum had a sub-hemispheric, microporous/hydroxyapatite double-coated design, which was conducive to early fixation and bone ingrowth. Corail femoral stems (DePuy, Warsaw, USA, 2018) were fully hydroxyapatite-coated and bio-type titanium alloy tapered. Summit femoral stems (DePuy, Warsaw, USA, 2018) were microporous/hydroxyapatite double-coated, proximally fixed, and bio-type titanium alloy tapered.

After successful anesthesia, an incision of about 12 cm was made, extended 5 cm outward from the lateral femur at the position between the greater trochanter and mid-lateral 1/3 of the line connecting the posterior superior iliac spine to the greater trochanter. The femoral neck was sawed off at 2 cm above the lesser trochanter, and the surrounding related ligaments and joint capsules were cut off. Then the femoral head was taken out, and the stump was reamed repeatedly. Finally, the acetabular prosthesis was placed.

Observation indices

The baseline data of patients, operation conditions, and incidence of adverse reactions were recorded.

The visual analog scale (VAS) score was given before nerve block (T_1), at 10 min after nerve block (T_2), at the time of position changing (T_3), and after position changing (T_4). The scoring system was – 0 points: no pain; ≤ 3 points: mild pain that can be tolerated; 4–6 points: pain affecting sleep; 7–10 points: severe pain that cannot be tolerated. The patient chose a number from 0 to 10 to represent their own pain degree. The higher the score, the more severe the pain.

At T_1, T_2, T_3, and T_4, the hemodynamic indices, heart rate (HR), and mean arterial pressure (MAP) were recorded.

At T_1, T_2, T_3, and T_4, the blood was drawn from the median cubital vein without receiving an intravenous injection, and plasma cortisol (COR) and epinephrine (E) were detected using a UniCel DXI800 automatic chemiluminescence immunoassay analyzer (Beckman Coulter, USA).

Statistical analysis

The experimental data were statistically analyzed using the SPSS 16.00 software (IBM Inc., USA, 2018). The count data were expressed as numbers (percentages) and compared by the chi-squared (χ^2) test. All measurement data were subjected to the homogeneity of variance and normal distribution tests, and the normally distributed data were expressed as mean ± standard deviation (SD). First, repeated measures analysis of variance was used to analyze the difference between the two groups and the time difference of each measured value. If there was a difference, the least significant difference (LSD)-*t*-test was further employed to compare the intergroup difference at each time point, and Newman-Keuls or Student-Newman-Keuls (SNK)-q-test was used to compare the time difference in each group. The value of $p < 0.05$ suggested a statistically significant difference.

Results

Baseline clinical data

There were no statistically significant differences in age, height, weight, gender ratio, chronic diseases, ASA grade, surgical site, and primary diseases between the two groups ($p > 0.05$) (Table 1).

Table 1

Baseline clinical data

Group	FICB (n = 45)	PNGB (n = 45)	t/χ^2	*p*
Age (years)	71.98 ± 5.84	72.46 ± 6.03	0.384	0.702
Height (cm)	165.12 ± 8.39	164.89 ± 8.27	0.131	0.896
Weight (kg)	54.73 ± 7.68	55.24 ± 7.79	0.313	0.755
Male	20 (44.4)	17 (37.78)	0.413	0.52
Female	25 (55.5)	28 (62.2)		
Chronic disease				
arrhythmia	16 (35.56)	19 (42.22)	0.421	0.517
hypertension	26 (57.78)	24 (53.33)	0.18	0.671
coronary heart disease	10 (22.22)	8 (17.78)	0.278	0.598
ASA grade				
I	34 (75.56)	37 (82.22)	0.6	0.438
II	11 (24.44)	8 (17.78)		
Surgical site				
left	20 (44.44)	22 (48.89)	0.179	0.673
right	25 (55.56)	23 (51.11)		
Primary disease				
femoral head necrosis	18 (40.00)	21 (46.67)	0.425	0.809
osteoarthritis	14 (31.11)	12 (26.67)		
coxitis	13 (28.89)	12 (26.67)		

Intergroup comparisons of measurement data: least significant difference (LSD)-*t*-test; intergroup comparisons of count data: χ^2 test.
FICB – fascia iliaca compartment block; PNGB – pericapsular nerve group block.
All values are expressed as mean ± standard deviation or numbers (percentages).

VAS scores

The VAS score had no statistically significant difference between the two groups at T_1 ($p > 0.05$), while it was lower in the PNGB group than that in the FICB group at T_2–T_4 ($p < 0.001$). The VAS score declined at T_2, rose at T_3, and dropped again at T_4 in the two groups, and the difference was statistically significant between any two adjacent time points ($p < 0.05$) (Table 2).

Hemodynamic indices

No statistically significant differences were found in HR and MAP between the two groups and at each time point ($p > 0.05$) (Table 3).

Stress responses

E and COR had no statistically significant differences between the two groups at T_1 ($p > 0.05$), while they were lower in the PNGB group than those in the FICB group at T_2–T_4 ($p < 0.001$). E and COR declined at T_2, rose at T_3, and dropped again at T_4 in the two groups, and the differences were statistically significant between any two adjacent time points ($p < 0.001$) (Table 4).

Operation conditions

There were no statistically significant differences between the two groups concerning the duration of puncture injection, operation time, and recovery time ($p > 0.05$). In the PNGB group, the ultrasonic imaging time was shorter, the time point of pressing PCA for the first time was later, and the numbers of pressing PCA were fewer, with statistically significant differences compared with the FICB group ($p < 0.001$) (Table 5).

Adverse reactions

No local anesthetic poisoning took place in either of the groups after the nerve block, and no hematoma at the puncture site, nerve injury, nausea and vomiting, dizziness, or delirium occurred after the operation.

Table 2

Visual analog scale (VAS) scores at different time points (T_1–T_4)

Group	T_1	T_2	T_3	T_4
FICB	5.71 ± 0.63	1.46 ± 0.52*	2.39 ± 0.75$^{*\#}$	1.58 ± 0.61^{*a}
PNGB	5.83 ± 0.67	0.29 ± 0.14*	1.17 ± 0.38$^{*\#}$	0.35 ± 0.17^{*a}
t	0.875	14.574	9.734	13.030
p	0.384	< 0.001	< 0.001	< 0.001

T_1 – VAS score before nerve block; T_2 – VAS score at 10 min after nerve block; T_3 – VAS score at the time of position changing; T_4 – VAS score after position changing. For other abbreviations, see Table 1.

* $p < 0.05$ vs. T_1; $^{\#}$ $p < 0.05$ vs. T_2; ^{a} $p < 0.05$ vs. T_3.

Number of patients = 90 (two groups of 45 patients).

All values are expressed as mean ± standard deviation.

Table 3

Hemodynamic indices at different time points (T_1–T_4)

Group	Heart rate (beats/min)				Mean arterial pressure (mmHg)			
	T_1	T_2	T_3	T_4	T_1	T_2	T_3	T_4
FICB	79.85 ± 14.56	76.37 ± 14.11	82.05 ± 15.86	78.24 ± 15.39	110.46 ± 13.82	105.27 ± 12.36	108.64 ± 13.12	106.53 ± 12.78
PNGB	80.24 ± 15.07	77.04 ± 14.25	79.68 ± 14.73	77.81 ± 14.56	109.78 ± 13.27	104.61 ± 12.05	107.59 ± 12.74	105.48 ± 12.16
t	0.125	0.224	0.735	0.136	0.238	0.256	0.385	0.399
p	0.901	0.823	0.465	0.892	0.812	0.798	0.701	0.691

For abbreviations see Tables 1 and 2.

Number of patients = 90 (two groups of 45 patients). All values are expressed as mean ± standard deviation.

Table 4

Stress responses at different time points (T_1–T_4)

Group	Epinephrine (ng/mL)				Cortisol (pg/mL)			
	T_1	T_2	T_3	T_4	T_1	T_2	T_3	T_4
FICB	58.37 ± 6.53	39.41 ± 4.86*	45.62 ± 5.47$^{*\#}$	40.39 ± 5.12^{*a}	201.45 ± 21.67	163.58 ± 17.49*	187.32 ± 19.83$^{*\#}$	170.68 ± 17.92^{*a}
PNGB	60.12 ± 6.69	31.25 ± 4.34*	37.78 ± 4.93$^{*\#}$	33.26 ± 4.48^{*a}	198.76 ± 20.85	132.37 ± 14.28*	159.61 ± 16.07$^{*\#}$	137.45 ± 14.53^{*a}
t	1.256	8.401	7.142	7.030	0.600	9.272	7.283	9.662
p	0.213	< 0.001	< 0.001	< 0.001	0.550	< 0.001	< 0.001	< 0.001

For abbreviations see Tables 1 and 2. * $p < 0.05$ vs. T_1; $^{\#}$ $p < 0.05$ vs. T_2; ^{a} $p < 0.05$ vs. T_3.

Number of patients = 90 (two groups of 45 patients). All values are expressed as mean ± standard deviation.

Table 5

Operation conditions at different time points (T_1–T_4)

Group	Ultrasonic imaging time (s)	Duration of puncture injection (s)	Operation time (min)	Recovery time (min)	Extubation time (min)	Time point of pressing PCA for the first time (h)	Number of pressing PCA
FICB	44.27 ± 9.63	104.39 ± 18.51	135.58 ± 19.72	12.46 ± 2.53	16.75 ± 2.94	11.73 ± 2.25	2.34 ± 0.64
PNGB	23.56 ± 7.82	103.16 ± 17.94	134.02 ± 18.96	11.85 ± 2.34	15.99 ± 2.86	30.98 ± 4.17	1.61 ± 0.45
t	11.199	0.320	0.383	1.187	1.243	27.253	6.259
P	< 0.001	0.750	0.703	0.238	0.217	< 0.001	< 0.001

PCA – patient controlled analgesia. For other abbreviations, see Tables 1 and 2.
Number of patients = 90 (two groups of 45 patients). All values are expressed as mean ± standard deviation.

Discussion

When there are no contraindications, the Guidelines on Anesthesia and Perioperative Management of Elderly Hip Fracture Patients in China recommend intraspinal anesthesia as the preferred anesthesia method in a completely lateral position; however, hip fracture patients are often unable to position themselves in such a way due to severe pain, thus increasing the difficulty of administering the anesthesia and reducing the success rate [8, 9]. It is reported in the literature that after local anesthetics are injected into the fascia iliaca compartment and diffused, they can simultaneously block the obturator nerve, femoral nerve, and lateral femoral cutaneous nerve, thereby exerting a good analgesic effect. Therefore, it is recommended that FICB be conducted on the affected side before positioning the patient [10, 11]. Girón-Arango et al. [12] anatomized the anterior hip articular capsule carefully and summarized the direction, distribution, and bony landmarks of the hip articular branch from the lumbar nerve branch based on which the latest anatomical research on hip innervation was published, and PNGB for a sensory block on the anterior hip articular capsule was further proposed. On patients with hip pain caused by different factors, 20 mL of local anesthetics had a good effect. Afterward, Tran et al. [13] applied 10 mL of dye solution for PNGB and found that the dye could completely wrap the anterior hip articular capsule. The above studies suggest that PNGB can be performed before positioning the patient receiving intraspinal anesthesia for hip replacement. A certain volume of local anesthetics is required to fully block the large fascia iliaca compartment, so 30 mL of 0.25% ropivacaine was injected in this study to avoid the research results being affected by the amount of anesthetics.

The effective analgesic duration of FICB can be up to 36–48 hrs. However, it has been found that FICB cannot completely block the obturator nerve, so there is often a problem of insufficient analgesia [14–17]. Cui et al. [18] showed that both FICB and PNGB could relieve well the acute early pain of elderly patients with hip fractures, but PNGB took effect quickly and had a better analgesic effect. The above reports were further supported by the results in this study because FICB has an incomplete blocking effect on the obturator nerve. During position changes, the pain was aggravated in the two groups, which is consistent with the study of Xie et al. [19]. Possibly, the posterior hip articular capsule is blocked insufficiently, and the hip fracture end shifts during position changes, stimulating the surrounding muscle tissues. According to the previous data, bradycardia and hypotension can occur when ropivacaine is epidurally injected [20–22]. In this study, HR and MAP fluctuated at each time point but kept certain stability in the two groups, and the possible reason is that only the effects of nerve block on HR and MAP were observed in this study. Moreover, 0.25% ropivacaine was used, which could maintain stable hemodynamics in FICB and PNGB.

Fracture trauma is one of the important causes of oxidative stress. Surgery with greater trauma and severe pain can aggravate the oxidative stress response, which is mainly manifested as the enhancement of COR secretion from the pituitary-adrenal cortex and E secretion from the adrenal medulla [23–25]. In this study, the changes in E and COR at different time points within and between the groups showed that both FICB and PNGB could effectively block the influx of peripheral injury stimuli and inhibit the sympathetic nerve excitement, thereby reducing the secretion of E and COR. On the contrary, the pain during position changing could also cause a certain degree of oxidative stress, thereby enhancing the secretion of E and COR. PNGB exerted a better analgesic effect to reduce the oxidative stress level, being in accordance with previous literature [26, 27]. In this study, the PNGB group had a shorter ultrasonic imaging time because it is easier to distinguish the bony landmarks used for positioning in PNGB. In FICB, the femoral artery is first found below the groin, and then the probe is moved outward and rotated. Moreover, due to loose tissues in elderly patients, the ultrasound image of the fascia iliaca compartment is unclear, so it takes a longer time. In both FICB and PNGB, 0.25% ropivacaine is injected into the nerve trunk to temporarily block the nerve conduction, exerting a regional anesthetic effect without blocking the visceral nerves in the abdominal and pelvic cavities. In addition, the nerve is accurately positioned under ultrasonic guidance without directly affecting the femoral nerve so that the occurrence of postoperative complications is reduced.

Conclusion

In conclusion, both FICB and PNGB have good safety prior to SAB in the elderly undergoing hip replacement; however, PNGB has shorter ultrasonic imaging time, a better analgesic effect, and a lower oxidative stress level, hence it is worthy of clinical popularization and application.

Conflict of interest

The authors declare no conflict of interest.

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Noninvasive assessment of the presence and size of esophageal varices

Neinvazivna procena postojanja i veličine varikoziteta jednjaka

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Abstract

Background/Aim. A significant number of patients with liver cirrhosis who underwent screening endoscopy do not have esophageal varices (EVs) or have EVs that do not require prophylactic therapy. Given the invasiveness of the procedure, the need to develop nonendoscopic methods in predicting the presence of EVs is reasonable. The aim of the study was to determine the significance of clinical, biochemical, and ultrasonic parameters in the prediction of EVs. **Methods**. The study included 59 patients with cirrhosis of the liver, 39 (66.1%) patients with EVs, and 20 (33.9%) patients without EVs. In the group of patients with EVs, 22 (56.4%) patients had small EVs, and 17 (46.3%) had large EVs. Clinical parameters that included Child-Pugh (CP) score, ascites, and splenomegaly were evaluated. In all participants, complete blood count, liver function tests, abdominal ultrasound, and gastroscopy were performed, and a platelet count/spleen diameter (PC/SD) ratio was calculated. **Results**. Univariate logistic regression analysis showed that independent risk factors for the occurrence of EVs were the following: CP B class [odds ratio (OR) 6.67; $p = 0.003$] and CP C class (OR 23.33; $p = 0.005$) relative to class A, ascites (OR 7.78; $p = 0.001$), spleen size (OR 1.035; $p = 0.016$), bilirubin (OR 1.065; $p = 0.007$), albumin (OR 0.794; $p = 0.001$), prothrombin time (OR 0.912; $p < 0.001$), international normalized ratio-INR (OR 231.364; $p < 0.001$), platelet count (OR 0.989; $p = 0.023$), and PC/SD ratio (OR 0.999; $p = 0.034$). In a multivariate model, it was shown that a decreased platelet count was a statistically significant risk factor for the presence of EVs (OR 0.983; $p = 0.023$). Leukopenia and the size of the right liver lobe were found to be statistically significant factors for the occurrence of large EVs. Based on the receiver operating characteristic (ROC) curve for the PC/SD ratio, the cutoff value of the test was obtained at 907 (907.11), with a negative predictive value of 76.4% for large EVs. **Conclusion.** The cutoff value of PC/SD ratio < 907 has a predictive value for the occurrence of large EVs.

Key words:
esophageal and gastric varices; liver cirrhosis; platelet count; prognosis; risk factors; spleen.

Apstrakt

Uvod/Cilj. Znatan broj bolesnika sa cirozom jetre podvrgnutih „skrining“ endoskopiji nema ezofagealne varikozitete (EV) ili ima EV za koje nije potrebna profilaktička terapija. Imajući u vidu invazivnost te procedure, razumljiva je potreba za razvojem neendoskopskih metoda za procenu prisustva EV. Cilj rada bio je da se utvrdi značaj kliničkih, biohemijskih i ultrazvučnih parametara u predviđanju EV. **Metode.** U istraživanje je bilo uključeno 59 bolesnika sa cirozom jetre, 39 (66,1%) bolesnika sa EV i 20 (33,9%) bolesnika bez EV. U grupi bolesnika sa EV 22 (56,4%) bolesnika imalo je male EV, a 17 (46,3%) bolesnika velike EV. Procenjivani su klinički parametri, koji su uključivali *Child-Pugh* (CP) klasu, prisustvo ascita i splenomegaliju. Svim ispitanicima urađeni su kompletna krvna slika, testovi funkcije jetre, ultrazvuk abdomena, gastroskopija i izračunat je odnos broja trombocita/dijametra slezine (*platelet count/spleen diameter* – PC/SD). **Rezultati.** Univarijanta logistička regresiona analiza pokazala je da su nezavisni faktori rizika od pojave EV bili: CP B klasa [*odds ratio* (OR) 6,67; $p = 0,003$] i CP C klasa (OR 23,33; $p = 0,005$) u odnosu na klasu A, prisustvo ascita (OR 7,78; $p = 0,001$), veličina slezine (OR 1,035; $p = 0,016$), bilirubin (OR 1,065; $p = 0,007$), albumin (OR 0,794; $p = 0,001$), protrombinsko vreme (OR 0,912; $p < 0,001$), *international normalized ratio*-INR (OR 231,364; $p < 0,001$), broj trombocita (OR 0,989; $p = 0,023$) i odnos PC/SD (OR 0,999; $p = 0,034$). U multivarijantnom modelu pokazalo se da je statistički značajan faktor rizika od prisustva EV bio smanjenje broja trombocita (OR 0,983; $p = 0,023$). Utvrđeno je da su statistički značajni faktori rizika od pojave velikih EV bili leukopenija i veličina desnog lobusa jetre. Na osnovu *receiver operating characteristic* (ROC) krive za odnos PC/SD, dobijena je granična (*cutoff*) vrednost testa 907 (907,11), sa negativnom prediktivnom vrednošću od 76,4% za velike EV. **Zaključak.** *Cutoff* vrednost odnosa PC/SD < 907 ima prognostički značaj za pojavu velikih EV.

Ključne reči:
jednjak i želudac, variksi; jetra, ciroza; trombociti, broj; prognoza; faktori rizika; slezina.

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Introduction

Portal hypertension (PH) is a common clinical syndrome, which is hemodynamically defined as a pathological increase in portal venous pressure. With the increase in portal venous pressure, the pressure gradient between the *inferior vena cava* and the portal vein increases as well (hepatic venous pressure gradient – HVPG), with the formation of portosystemic collaterals that divert the portal bloodstream to the systemic circulation, bypassing the liver. The normal HVPG value is 1–5 mmHg. PH is the result of an increase in resistance or blood flow in the portal vein. Any process that disrupts blood flow at any level of the portal venous system can cause PH. Liver cirrhosis (LC) causes more than 90% of cases of PH in Western countries [1–5].

Patients with LC go through two different stages of the disease, through compensated and decompensated cirrhosis. Depending on the pressure level at the level of the portal system, patients with PH and LC may be divided into patients with mild or subclinical PH (HVPG gradient > 5 mmHg, < 10 mmHg) and patients with clinically significant PH (CSPH), defined by an increase in HVPG ≥ 10 mmHg. Above this critical threshold, patients are at increased risk of developing clinical decompensation of the disease and complications, gastroesophageal varices (GEVs), ascites, variceal bleeding (VB), and encephalopathy [6, 7]. GEVs are the most relevant portosystemic collaterals because VB caused by wall rupture of the varix is the most common complication of LC with a fatal outcome. GEVs are present in 50% of patients with LC. The most significant predictor of esophageal varices (EVs) occurrence in patients who had no EVs at initial endoscopy is an increase in HVPG above 10 mmHg. Patients with HVPG over 12 mmHg, especially over 16 mmHg, are at increased risk of bleeding from EVs and have an increased mortality rate. Bleeding from GEVs is the cause of more than 70% of gastrointestinal bleeding events in patients with PH. An increase in HVPG over 20 mmHg is the most significant risk factor for early rebleeding (within one week of initial bleeding) (83% vs. 29%), treatment failure (64% vs. 20%), and one-year mortality compared to the period when HVPG is lower. The risk of variceal hemorrhage is 5% to 15% *per* year. It is important to understand that every patient with HVPG higher than 12 mmHg does not bleed from varices. Other important prognostic indicators of the risk of VB are the Child-Turcotte-Pugh score, the size of varices, and the presence of red signs on varices, such as hematocystic spots and blue-colored varices [1, 8–12].

The only reference method of quantifying the severity of PH is measuring the gradient of hepatic venous pressure. All portal pressure measurement methods are invasive. An indirect, less invasive method measures the "wedged" hepatic venous pressure (WHVP) by balloon catheterization of the hepatic vein. Despite its accuracy, this method, due to its invasiveness and limited availability in hospitals, has led to the development of noninvasive diagnostic tests and procedures of varying sensitivity [6, 13, 14].

The next "gold standard" in evaluating PH is the upper gastrointestinal endoscopy for the detection of GEVs, which is essential in the treatment of VB. Annually, 7%–8% of patients with compensated LC develop EVs, and in 8–12% of patients, progression from small to large EV is recorded. Given the dynamics of HVPG over time, accompanied by clinical worsening of the disease, patients with LC should undergo endoscopy at the time of diagnosis as well as periodic endoscopies [1, 13, 15, 16].

Patients repeatedly undergo an uncomfortable, invasive procedure with associated risks, although half of the patients do not have recognizable varices even ten years after the diagnosis of LC [17]. Today, significant efforts are being made to detect noninvasive tests that would identify patients with LC and low risk of the presence of varices.

Studies have shown that serum hepatic insufficiency markers such as hypoalbuminemia, prolonged prothrombin time, hyperbilirubinemia, and stratification of patients based on Child-Pugh (CP) correlate with clinically significant PH and presence/degree of varicosity. Patients with CP class B and C have a three-fold higher risk of developing varices compared to patients with CP class A, including the presence of large varices [18].

By integrating two parameters, platelet count and craniocaudal spleen diameter measured by ultrasound, a new pathophysiologically important parameter was obtained that can be easily calculated and used in clinical practice as the EVs screening method. Given that spleen diameter and platelet count measurements are part of the routine treatment of patients with LC, the costs would be lowered, while patients would be spared the inconvenience of exposure to endoscopy [19].

The aim of our research was to identify the clinical, biohumoral, and ultrasonographic predictors of the presence and size of EVs in patients with LC.

Methods

Retrospective research was conducted at the Clinic for Gastroenterology and Hepatology of the University Clinical Center Niš. Serbia. This study was approved by the Ethics Committee of this institution.

The study included 59 patients over 18 years of age diagnosed with LC of different etiology, using adequate immunoassays and determining antibodies for hepatitis B and C viruses. Patients who had consumed more than 50 g of alcohol *per* day for at least five years were diagnosed with alcoholic cirrhosis of the liver. In cases where the etiologic factor of the disease was not detected, LC was classified as cryptogenic. In the study, there were no patients with hereditary or metabolic liver diseases.

Patients with bleeding from EVs at the time of examination, patients who had previously bled and had sclerosis of EVs or band ligatures, and patients with already diagnosed hepatocellular carcinoma were not included in the study.

Physical examination evaluated the presence of ascites, splenomegaly, hepatomegaly, spider angioma, and hepatic encephalopathy.

In laboratory blood analyses, complete blood count was performed; the values of aspartate aminotransferase (AST), al-

anine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total and direct bilirubin, urea, creatinine, proteins, albumins, prothrombin time, and international normalized ratio (INR) were obtained.

An ultrasound examination of the abdomen was performed during the morning hours using an ultrasound probe of 3.5 MHz, which was preceded by fasting the night before the examination.

The position, shape, contours, and echostructure of the liver parenchyma were evaluated, and the size of the right lobe in the medioclavicular line expressed in mm was measured. The size of the spleen was determined by measuring its largest longitudinal diameter expressed in mm. The presence of ascites was assessed. Using the platelet count and maximum longitudinal spleen diameter (PC/SD) ratio for each patient was calculated [19, 20].

The assessment of liver function was performed using the CP classification. The classification includes two clinical parameters (ascites size and degree of hepatic encephalopathy) and four biochemical parameters (serum bilirubin and albumin levels and plasma levels of prothrombin time and INR). For each indicator, values are numerically individually classified into one of the categories, and each category brings a possible sum of points of 1–3. The total sum of points, which ranges from 5–15 depending on the values of the aforementioned parameters, classifies patients into three categories: A, B, or C. The patient belongs to Group A if the total number of points is 1–6, Group B if the score is from 7–9, and Group C if the score is greater than 9 [21].

Proximal video-endoscopy was performed in the endoscopy room of the Clinic for Gastroenterology and Hepatology of the University Clinical Center Niš. During the endoscopic examination, the presence and size of EVs, the presence of gastric varices, portal hypertensive gastropathy (PHG), and endoscopic signs indicating a risk of bleeding (cherry red spots) were assessed. The size of EVs during endoscopy was classified into three degrees: Grade 1 EVs – minimally penetrate the esophageal lumen and can be flattened by air insufflation but do not disappear; Grade 2 EVs – occupy less than 50% of the esophageal lumen; Grade 3 EVs – occupy more than half of the lumen, being confluent within the esophageal circumference [22].

Grade 1 EVs are considered "small" EVs, whereas grade 2 and 3 EVs are considered "large". For the purposes of this study, patients were divided into a group of patients without EVs and a group of patients with EVs. The group of patients with EVs was further divided into a group with "small" EVs and a group with "large" EVs.

Statistical analysis

Data are given as arithmetic mean and standard deviation and as numbers (percentages) of categorical data. The comparison of continuous variables between the two groups was performed using the *t*-test and Mann-Whitney *U* test. Categorical data were analyzed using the Chi-squared (χ^2) test. The testing of potential risk factors for the presence and size of EVs was performed by logistic regression analysis. GGT was excluded from the multivariate model due to multicollinearity. The discriminant ability of the PC/SD ratio was assessed by the receiver operating characteristic (ROC) curve. The hypothesis was tested with a significance threshold of $p < 0.05$. Statistical data analysis was performed in the program package R.

Results

Results related to the occurrence of esophageal varices

The study included 59 patients with LC, 39 (66.1%) patients with EVs, and 20 (33.9%) patients without EVs. The mean age of the patients with and without EVs was 60.28 ± 8.73 years and 57.10 ± 10.69 years, respectively. The groups were matched for age and gender ($p = 0.259$, $p = 0.972$). The male gender prevailed in both groups, with 69.2% in the group with EVs, i.e., 65.0% in the group without EVs.

Table 1

Clinical characteristics related to the presence of esophageal varices (EVs)

Parameters	With EVs	Without EVs	p^1
Etiology			
alcoholic	25 (64.1)	9 (45.0)	0.337
cryptogenic	8 (20.5)	3 (15.0)	
primary biliary cirrhosis	2 (5.1)	2 (10.0)	
hepatitis B virus	1 (2.6)	2 (10.0)	
hepatitis C virus	3 (7.7)	3 (15.0)	
autoimmune	0 (0.0)	1 (5.0)	
Child-Pugh class			
A	9 (23.1)	15 (75.0)	< 0.001
B	16 (41.0)	4 (20.0)	
C	14 (35.9)	1 (5.0)	
Encephalopathy	13 (33.3)	3 (15.0)	0.234
Cherry red spots	2 (5.1)	0 (0.0)	0.544
Portal hypertensive gastropathy	29 (74.4)	6 (30.0)	0.003
Spider angioma	8 (20.5)	3 (15.0)	0.872
Ascites	30 (76.9)	6 (30.0)	0.001
large	19 (63.3)	4 (66.7)	1.000
small	11 (36.7)	2 (33.3)	

All values are expressed as numbers (percentages). [1] Chi-squared test.

In the group of patients with EVs, 25 (64.1%) had alcoholic cirrhosis of the liver, 8 (20.5%) had cryptogenic LC, 3 (7.7%) had hepatitis C virus LC, 2 (5.1%) had primary biliary cirrhosis, and 1 had hepatitis B virus LC. Alcohol LC was also the most prevalent in the group of patients without EVs, in 9 (45%) patients. It was found that there was no statistically significant difference in the etiology of LC with reference to the presence of EVs ($p = 0.337$) (Table 1).

In the group of patients with EVs, 16 were in CP class B, 14 were in CP class C, and 9 patients were in CP class A. In the group of patients without EVs, 15 were in CP class A, 4 were in CP class B, and 1 was in CP class C. In the group of patients with EVs, CP class B (41.0%) and C (35.9%) dominated, while CP class A was dominant in the group without EVs (75.0%). There was a statistically significant difference in the frequency of different classes in relation to the presence of EVs ($p < 0.001$) (Table 1). In the group of patients with EVs, 30 had ascites diagnosed by ultrasound. In the group of patients without EVs, in most of them, ascites was not diagnosed with ultrasound. The frequency of ascites was statistically significantly larger in patients with EVs compared to patients without EVs (76.9% vs. 30.0%; $p = 0.001$). Thirteen patients with EVs had hepatic encephalopathy, while in the group without EVs, only three patients had this diagnosis. Spider angioma was found in eight patients with EVs and in three patients without EVs. The frequency of encephalopathy ($p = 0.234$) and spider angioma ($p = 0.872$) was nonsignificantly different compared to the presence of EVs (Table 1).

A comparison of routine laboratory and ultrasound parameters showed that AST, ALT, ALP, and GGT values were nonsignificantly different compared to the presence of EVs ($p = 0.737$, $p = 0.592$, $p = 0.361$, $p = 0.313$, respectively). Bilirubin values were statistically significantly higher in patients with EVs ($p = 0.001$). Albumin values were statistically significantly lower in patients with EVs ($p < 0.001$). Prothrombin time and platelet count were statistically significantly lower in patients with EVs ($p < 0.001$ and $p = 0.023$, respectively). INR values were statistically significantly higher in patients with EVs ($p < 0.001$). Leukocyte count did not differ statistically significantly in relation to the study groups ($p = 0.255$). PC/SD ratio values were statistically significantly lower in patients with EVs ($p = 0.025$). The size of the spleen was statistically significantly larger in patients with EVs compared to those who did not develop them ($p = 0.017$) (Table 2).

Univariate logistic regression analysis showed that independent risk factors for EVs were: PHG [odds ratio (OR) 6.77; $p = 0.002$], CP B class (OR 6.667; $p = 0.003$) and CP C class (OR 23.333; $p = 0.005$) relative to class A, ascites (OR 7.778; $p = 0.001$), spleen size (OR 1.035; $p = 0.016$), bilirubin values (OR 1.065; $p = 0.007$), albumin (OR 0.794; $p = 0.001$), prothrombin time (OR 0.912; $p < 0.001$), INR (OR 231.364; $p = 0.001$), platelet count (OR 0.989; $p = 0.023$), and PC/SD ratio (OR 0.999; $p = 0.034$). In a multivariate model, it was shown that a decrease in platelet count was a statistically significant risk factor for the presence of EVs. A decrease in platelet count by one unit led to a statistically significant 2% increase in the risk of EVs (OR 0.983; $p = 0.023$) (Table 3).

Based on the ROC curve for PC/SD ratio, the limit value of the test was obtained: 1,013 (1,013.82). The area under the ROC curve was 0.687 (0.540–0.833), ($p = 0.025$) (Figure 1). For the calculated parameters, the following values were obtained: sensitivity of 84.6%, specificity of 46.7%, positive predictive value of 56.4%, negative predictive value of 78.9%, and diagnostic efficiency of 63.8%.

Table 2

Biochemical and ultrasound parameters related to the presence of esophageal varices (EVs)

Parameters	Reference range (units)	With EVs	Without EVs	p[1]
AST	10–31 (U/L)	77.37 ± 58.27	78.05 ± 47.11	0.737
ALT	10–35 (U/L)	34.37 ± 18.23	40.9 ± 28.55	0.592
ALP	30–120 (U/L)	125.21 ± 56.74	164.18 ± 187.63	0.361
GGT	0–38 (U/L)	252.68 ± 381.28	261.41 ± 318.75	0.313
Bilirubin	5–20 (μmol/L)	45.69 ± 34.68	20.88 ± 13.16	0.001
Albumin	35–42 (g/L)	31.56 ± 4.62	37.81 ± 5.87	< 0.001[2]
Urea	2.5–7.5 (μmol/L)	5.49 ± 2.94	5.69 ± 2.52	0.642
Creatinine	53–115 (μmol/L)	81.05 ± 18.58	80.19 ± 17.79	0.823[2]
Prothrombin time	75–120 (%)	51.33 ± 12.32	80.71 ± 26.09	< 0.001
INR	0.8–1.2	1.54 ± 0.24	1.25 ± 0.28	< 0.001
Platelets	120–380 (× 10^9/L)	141.74 ± 59.04	183.6 ± 67.36	0.023
Leukocytes	4.0–9.0 (× 10^9/L)	7.07 ± 2.94	6.12 ± 1.81	0.255
PC/SD ratio	/	1,017.21 ± 484.42	1,320.54 ± 451.22	0.025
Right liver lobe	/	168.69 ± 26.16	165.25 ± 22.44	0.601[2]
Spleen	/	145.35 ± 20.43	129.90 ± 23.32	0.017[2]

AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alanine phosphatase; GGT – gamma-glutamyl transpeptidase; INR – international normalized ratio; PC/SD – platelet count/spleen diameter.

All values are expressed as arithmetic mean ± standard deviation.

[1] Mann-Whitney *U* test; [2] *t*-test.

Table 3

Risk factors for the presence of esophageal varices – logistic regression analysis

Risk factor	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*	OR	95%CI	*p*
Gender	1.212	0.386–3.800	0.742			
Age	1.036	0.978–1.098	0.225			
PHG	6.77	2.046–22.384	0.002			
Child-Pugh class						
A		RG			RG	0.710
B	6.667	1.690–26.298	0.191	3.546	0.533–23.600	0.191
C	23.333	2.610–208.616	0.230	5.730	0.331–99.336	0.230
Spider angioma	1.462	0.342–6.252	0.608			
Ascites	7.778	2.314–26.141	0.001	6.731	0.668–67.852	0.106
Right lobe	1.006	0.984–1.028	0.612			
Spleen	1.035	1.006–1.064	0.016	1.013	0.978–1.049	0.475
AST	1.000	0.990–1.010	0.964			
ALT	0.987	0.964–1.011	0.292			
ALP	0.997	0.993–1.002	0.256			
GGT	1.000	0.998–..001	0.929			
Bilirubin	1.065	1.018–1.114	0.007			
Albumin	0.794	0.696–0.905	0.001			
Urea	0.976	0.804–1.184	0.802			
Creatinine	1.003	0.973–1.033	0.863			
Prothrombin time	0.912	0.869–0.958	< 0.001			
INR	231.364	9.762–5483.54	0.001			
Platelets	0.989	0.980–0.999	0.023	0.983	0.969–0.998	0.023
Leukocytes	1.156	0.930–1.438	0.192			
PC/SD ratio	0.999	0.997–1.000	0.034			

OR – odds ratio; CI – confidence interval; RG – reference group; PHG – portal hypertensive gastropathy. For other abbreviations, see Table 2.

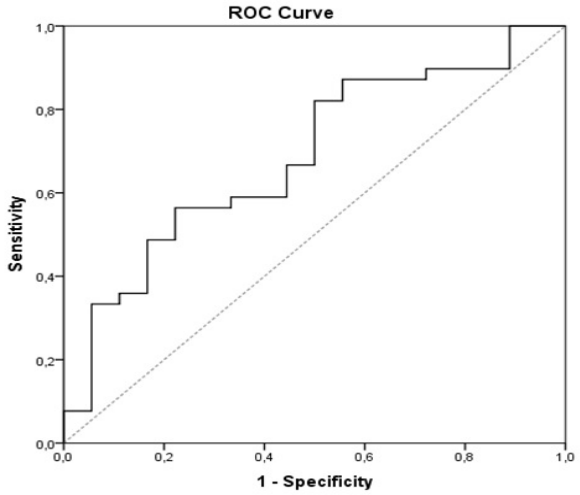

Fig. 1 – Receiver operating characteristics (ROC) curve for platelet count/spleen diameter values related to the occurrence of esophageal varices.

Results related to the size of esophageal varices

In the group of patients with EVs, 22 (56.4%) patients had small EVs, and 17 (46.3%) patients had large EVs. The univariate logistic regression analysis showed that independent risk factors for the size of EVs were: the size of the right liver lobe (OR 0.960, $p = 0.011$), leukocyte count (OR 0.689, $p = 0.009$), and PC/SD ratio (OR 0.998, $p = 0.045$) (Table 4). In the multivariate model, the size of the right liver lobe and leukocyte count, corrected for all other parameters in the model (OR 0.691, $p = 0.027$), were distinguished as statistically significant risk factors for the occurrence of large EVs.

Based on the ROC curve for PC/SD ratio in relation to the size of EVs, the obtained limit value of the test was 907 (907.11). The area under the ROC curve was 0.698 (0.524–0.872, $p = 0.036$). Sensitivity of 80.0%, specificity of 68.4%, positive predictive value of 72.7%, negative predictive value of 76.5%, and diagnostic test efficiency of 74.4% were obtained for the calculated parameters (Figure 2).

Table 4

Risk factors for the presence of large esophageal varices – logistic regression analysis

Parameter	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*	OR	95%CI	*p*
Gender	0.688	0.175–2.699	0.591			
Age	1.029	0.954–1.111	0.453			
Child-Pugh class						
A		RG				
B	0.568	0.105–3.070	0.511			
C	1.667	0.308–9.014	0.553			
PHG	4.286	0.773–23.746	0.096	4.908	0.535–44.995	0.159
Encephalopathy	3.022	0.761–11.999	0.116			
Spider angioma	2.639	0.531–13.116	0.236			
Ascites	0.956	0.213–4.284	0.953			
Right liver lobe	0.960	0.931–0.991	0.011	0.959	0.924–0.996	0.029
Spleen	1.002	0.971–1.034	0.892			
AST	0.999	0.987–1.010	0.814			
ALT	1.000	0.965–1.034	0.982			
ALP	0.995	0.983–1.007	0.409			
GGT	0.994	0.987–1.001	0.070			
Bilirubin	0.986	0.964–1.008	0.211			
Albumin	0.972	0.845–1.118	0.690			
Urea	1.082	0.868–1.350	0.482			
Creatinine	1.030	0.992–1.069	0.122			
Prothrombin time	0.952	0.897–1.011	0.109			
INR	5.874	0.337–102.406	0.225			
Platelets	0.988	0.975–1.000	0.051	1.011	0.961–1.063	0.668
Leukocytes	0.689	0.520–0.912	0.009	0.691	0.498–0.959	0.027
PC/SD ratio	0.998	0.997–1.000	0.045	0.998	0.992–1.005	0.589

OR – odds ratio; CI – confidence interval; RG – reference group; PHG – portal hypertensive gastropathy. For other abbreviations, see Table 2.

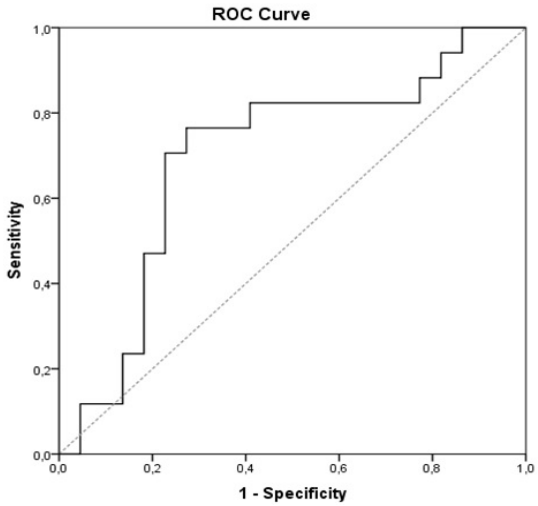

Fig. 2 – Receiver operating characteristics (ROC) curve for platelet count/spleen diameter values related to the size of the esophageal varices.

Discussion

Bleeding from EVs is one of the most urgent conditions in medicine, followed by high morbidity and mortality rates, which is 20% in the first six weeks after bleeding. The risk of VB in PH depends on the degree of PH, liver failure, size of EVs, and endoscopic appearance of EVs. Based on clinical and endoscopic characteristics, The North Italian Endoscopic Club described a formula for predicting the risk of the first episode of VB based on CP class (CP B/C), the size of EVs, and the presence of red spots on the surface of EVs [15, 23].

Given that VB can be prevented with the use of nonselective beta-blockers or band ligature, early diagnosis of EVs is essential when evaluating patients with LC.

Proximal endoscopy is the gold standard in diagnostics, grading, and assessment of surface EVs. All patients diagnosed with LC should undergo proximal endoscopy at the

time of diagnosis. Screening endoscopies are recommended at the time interval of one to three years, depending on the degree of hepatic insufficiency, presence and size of EVs, persistence of the etiological factor of the disease, and comorbidity [24].

Most patients who have undergone a screening endoscopy either have no EVs or have EVs that do not require prophylactic therapy [11]. The disadvantages of endoscopy include the risk of sedation, higher costs, bleeding, and the risk of aspiration.

Today, clinicians have an interest in identifying the "ideal" noninvasive markers that would be inexpensive, easy to perform, and easily reproducible but with high specificity and sensitivity, which would reduce the number of screening and therapeutic endoscopies in patients with EVs and cirrhosis of the liver. Such noninvasive parameters are particularly needed in developing countries with limited resources and a lack of a sufficient number of endoscopy rooms [25].

In 2003, Giannini et al. [19] recommended the use of the PC/SD ratio as a single noninvasive test that is easily calculated on the basis of parameter values that are part of a routine diagnostic assessment of patients with LC. This test with the cutoff value of 909 was found to have 100% sensitivity, 100% negative predictive value, and a specificity of 93% for EVs, which would meet the criteria of an ideal noninvasive test. Many other noninvasive markers and PC/SD ratios were calculated and correlated with esophagogastroduodenoscopy findings in many other studies with different cutoffs and predictive values for EVs [25–27]. In patients with PH, the risk of the first-time VB or rebleeding was significantly associated with the PC/SD ratio [10]. The meta-analyses of the studies whose subject matter was the PC/SD relationship did not confirm the previous allegations [28, 29].

Today, liver stiffness measurement (LSM) by transient elastography (TE) is among the best-validated noninvasive markers of liver fibrosis. Results of LSM showed a close correlation with HVPG and good accuracy (AUC = 0.93) in diagnosing PH. LSM value < 13.6 kPa assessed by TE resulted valuable to rule-out CSPH with high sensitivity (> 90–95%). More than 90% of patients with an LSM > 20–25 kPa will have clinically significant PH (specificity > 90–95%). One of the most important applications of elastometry is the identification of patients with GEVs. LSM is considered to have high sensitivity but medium or low specificity in predicting EVs in several studies [30].

A combination of measurement of liver stiffness and platelet count increases the predictive value of the method and is incorporated in the Baveno VI guidelines. In patients with chronic advanced liver disease, the Baveno VI consensus conference recommended that patients with normal platelet count (>150,000 /μL) and liver stiffness less than 20 kPa measured by TE should not undergo screening endoscopy. This strategy is safe and allows the saving of 15–25% of unnecessary endoscopies. The strategy only applies to well-compensated patients (compensated advanced chronic liver disease – cACLD), while patients with decompensated LC should undergo endoscopy regardless of the platelet count. That is a great improvement as it reduces costs and provides monitoring of varices less stressful for patients. Measuring platelet count is part of the routine laboratory processing of patients with LC, but the patient's constitution, lack of equipment, and trained personnel limit the use of TE [15, 25, 31].

The newer expanded Baveno VI criteria proposed new cutoff values for platelet count > 110×10^9 cells/L and LSM < 25 kPa to spare even more endoscopies with minimal risk of missing high-risk EVs in patients with cACLD [32, 33].

Splenomegaly is a common finding in patients with LC. Colecchia et al. [34] first demonstrated a clear and strong correlation between spleen stiffness measurement (SSM) by TE and the presence and degree of PH assessed by HVPG. With a cutoff value of < 40 kPa, the presence of CSPH and EVs can be ruled out with a sensitivity of 98.5 %. A recent meta-analysis confirmed that SSM has a strong correlation with the whole range of HVPG values and was quite useful for ruling out the presence of high-risk EVs [35, 36].

A combination of Baveno VI criteria and SSM (cut-off ≤ 46 kPa, assessed by TE) is another new diagnostic model which proved efficient in increasing the number of spared endoscopies without raising the rate of missed high-risk EVs [37].

TE is safe, reliable, and easy to use, but it is still not universally available to patients, and its application has some limitations. Therefore, there is still a need for other simple and reliable noninvasive tests.

In our study, a univariate logistic regression analysis singled out the parameters related to PH (spleen size, ascites, platelets) and parameters related to liver dysfunction or advanced disease (CP class B and C, serum bilirubin, albumins, prothrombin time), and PC/SD ratio as significant parameters for the occurrence of EVs. Our results are in agreement with the results of other authors [19, 28]. Cherian et al. [38] determined in a univariate analysis that the PC/SD ratio ≤ 666 is a significant predictor of the presence of EVs in predominantly alcoholic LC. This relationship had no statistical significance in the multivariate model. In the study by de Mattos et al. [39], thrombocytopenia, splenomegaly, PC/SD ratio, CP class, Model for End-Stage Liver Disease (MELD) score, and the presence of ascites were significantly associated with the presence of EVs. The multivariate analysis determined thrombocytopenia as the only independent factor for the presence of EVs, which is consistent with our findings.

A study by Nemichandra et al. [40] showed that the factors influencing the occurrence of EVs are the following: thrombocytopenia, decreased serum albumin levels, decreased PC/SD ratio, as well as splenomegaly, higher bilirubin levels, prothrombin time, and greater diameter of the portal vein. A multivariate analysis identified the PC/SD ratio < 1,433.1 and splenomegaly as independent predictors associated with the presence of EVs.

In our study, the multivariate analysis singled out thrombocytopenia as an independent predictive factor for the occurrence of EVs, which is in line with the results of other authors [18, 38, 41, 42].

The PC/SD ratio limit value of 1,013 was obtained based on the ROC curve. The area under the ROC curve was 0.687. For the calculated parameters, a sensitivity of 84.6%, specificity of 46.7%, positive predictive value of 56.4%,

negative predictive value of 78.9%, and diagnostic efficiency of 63.8% for predicting EVs were obtained.

A similar cutoff value of the PC/SD ratio for predicting EVs was determined by Baig et al. [43]. Compared to our results, the test had a higher sensitivity of 98.1%, specificity of 88.6%, negative predictive value of 95.4%, and the area under the curve (AUC) was 0.942, which indicated excellent diagnostic accuracy.

The univariate logistic regression analysis singled out the right liver lobe, leukocyte count, and PC/SD ratio as independent risk factors for the occurrence of large EVs. The multivariate logistic regression analysis found that the right liver lobe and leukocyte count were independent predictors of large EVs. In the study by Sharma and Aggarwal [44], a univariate analysis also singled out the diameter of the right liver lobe and leukocyte count as risk factors for the occurrence of large EVs, as well as the platelet count and splenomegaly. In the multivariate model, splenomegaly and platelet count were distinguished as independent predictors of larger EVs [44].

In our research, based on the ROC curve, the PC/SD ratio limit value of 907 was obtained, with a sensitivity of 80%, specificity of 68.4%, positive predictive value of 72.7%, negative predictive value of 76.5%, and diagnostic efficiency of the test of 74.4% for the prediction of large EVs (AUC 0.698). In the study by Barrera et al. [45], the cutoff value of the PC/SD ratio for the prediction of high-risk EVs was 830.8. The sensitivity of the test was 76.9%, the specificity was 74.2%, and the negative predictive value was 77.8% (AUC 0.78), which is in line with our results.

Our study had some limitations. The main limitations are the retrospective nature of the data, the recruitment of patients from a single center, and the relatively small number of patients included in the final analysis.

Conclusion

In summary, this study showed that splenomegaly and thrombocytopenia are predictive factors for the presence of EVs. Leucopenia and the size of the right lobe of the liver are independent predictors of the presence of high-risk EVs. There was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in the PC/SD ratio. Our results indicate that the PC/SD ratio < 907 in patients with LC could be used as a noninvasive predictor of the presence of moderate to large EVs in patients with LC and should be considered a useful, simple method in identifying patients with LC at high risk of VB. A combination of all these predictors can help develop more effective and useful noninvasive methods for assessing the presence of high-risk EVs, which would improve surveillance of these patients and decrease the need for endoscopy.

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Assessment of location and anatomical characteristics of lingual foramen using cone beam computed tomography

Procena lokalizacije i anatomskih karakteristika lingvalnog foramena primenom kompjuterizovane tomografije konusnog zraka

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Abstract

Background/Aim. A lingual foramen (LF) is a small opening on the lingual surface of the mandible, most frequently located in the middle of the anterior part of the mandible, and shows significant variations in its location, size, and number. The aim of this study was to assess the location and anatomical characteristics of LF using cone beam computed tomography (CBCT). **Methods.** The research was designed as a retrospective study in which 99 CBCT scans were analyzed. The analysis covered the number of LF, their location concerning the teeth and the mandibular region itself, diameter, distance from the alveolar ridge crest, distance from the inferior border of the mandible, distance from the tooth apex, and position in relation to the tooth apex. **Results.** The average frequency of LF *per* patient was 2.4 ± 1.2. The largest number of LF were localized in the region of lower central incisors. Out of the total number of LF, 82.5% belonged to median LF, while 17.5% belonged to lateral LF. In 63.2% of cases, LF had a diameter of ≤ 1 mm, whereas, in 98.3% of cases, it was localized below the tooth apex. There was a statistically significant difference in the distance of LF from the alveolar ridge crest and the LF diameter in relation to gender ($p = 0.019$; $p = 0.008$). **Conclusion.** LF can be reliably localized and visualized using CBCT. It is recommended that CBCT scanning of the mandible be used while planning an oral surgical procedure and implant placement in order to prevent injuries of the neurovascular bundle, which passes through LF.

Key words:
anatomy; cone-beam computed tomography; mandible.

Apstrakt

Uvod/Cilj. Lingvalni foramen (LF) je mali otvor na lingvalnoj površini mandibule (donje vilice), najčešće lokalizovan u sredini anteriornog dela mandibule, koji pokazuje značajne varijacije u lokalizaciji, veličini i broju. Cilj rada bio je da se procene lokalizacija i anatomske karakteristike LF primenom kompjuterizovane tomografije konusnog zraka (KTKZ). **Metode.** Istraživanje je dizajnirano kao retrospektivna studija, u kojoj je analizirano 99 snimaka dobijenih primenom KTKZ. Analiziran je broj LF, njihova lokalizacija u odnosu na zube i samu regiju mandibule, dijametar, udaljenost od vrha alveolarnog grebena, udaljenost od donje ivice mandibule, udaljenost od vrha korena zuba, položaj u odnosu na vrh korena zuba i pravac pružanja. **Rezultati.** Prosečna zastupljenost LF po ispitaniku iznosila je 2,4 ± 1,2. Najveći broj LF bio je lokalizovan u regiji donjih centralnih sekutića. Od ukupnog broja LF, 82,5% pripadalo je tipu medijalnog LF, dok je 17,5% pripadalo tipu lateranog LF. U 63,2% slučajeva LF je imao prečnik ≤ 1 mm, dok je u 98,3% bio lokalizovan ispod vrha korena zuba. Utvrđena je statistički značajna razlika u udaljenosti LF od vrha alveolarnog grebena i dijametru LF u odnosu na pol ($p = 0{,}019$; $p = 0{,}008$). **Zaključak.** Metodom KTKZ snimanja, LF se može pouzdano lokalizovati i vizualizovati. Da bi se sprečile povrede neurovaskulrnog snopa koji prolazi kroz LF, preporuka je da se prilikom planiranja oralne hirurške i implantološke procedure koristi KTKZ mandibule.

Ključne reči:
anatomija; kompjuterizovana tomografija konusnog zraka; mandibula.

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Introduction

A lingual foramen (LF) is a small opening on the lingual surface of the mandible, most frequently located in the middle of the anterior part of the mandible, and shows significant variations in its location, size, and number [1, 2]. It can be located on the mandibular midline or near it [median lingual foramen (MLF)] or laterally [lateral lingual foramen (LLF)] [1, 3, 4]. When it is located on the mandibular midline, it can be under or above the mental spine [5].

The anterior part of the mandible is considered a safe region for surgical interventions and implant placement due to the absence of large neurovascular structures and good bone density [1, 6–10]. Nevertheless, the area between mental foramina must deserve greater attention, especially concerning anatomical structures present in this region [7, 11]. This region has blood vessels that may be diverse and result from the branches of the external carotid artery, lingual artery, and facial artery [12, 13]. Some data indicate the formation of an enlarging hematoma caused by an injury of LF [1, 14]. A review of the literature identified 19 cases of a serious hematoma connected with the placement of implants located between mental foramina [6]. The cases of sublingual hematoma were recorded after some oral surgical procedures, including osteotomy, tooth extraction, and biopsy of the floor of the mouth [15]. Special importance is given to the communication between the sublingual and submandibular spaces in their distal portion, where, due to the expansion of a hematoma airway, obstruction occurs [16, 17]. Flanagan [3] stated that 420 mL of blood can flow from an artery with an inner diameter of 1 to 2 mm in 30 min.

By dissecting cadaver mandibles, Liang et al. [18] showed that the MLF placed superior to the mental spine can contain a lingual artery, vein, and nerve. The branches of the mylohyoid nerve, sublingual and submental arteries, and veins can be found in the MLF placed inferior to the mental spine. Furthermore, the final branches of the incisive nerve enter the composition of the MLF, i.e., mandibular foramen [19]. The vascular bundle of the LLF comes from the submental artery and the inferior alveolar artery [20]. The inferior alveolar nerve is part of the LLF, i.e., mandibular foramen [1].

The introduction of cone beam computed tomography (CBCT) has considerably advanced radiological diagnostics and planning of surgical procedures in oral and maxillofacial surgery [21]. It is difficult to visualize LF in conventional radiographs [22, 23]. CBCT exceeds the limitations of conventional radiography by producing undistorted three-dimensional images of the area under examination [24]. The error rate of CBCT displaying bony structures is less than 1%, whereas the error rate in panoramic radiographs is more than 30% [1]. The bony canals on the lingual surface of the mandible can be clearly observed from several different perspectives in CBCT scans [6]. It is supported by the fact that CBCT scanning results in accuracy are equal to that produced by direct visualization of anatomical structures in the mandible [25]. Preoperative analysis of LF is significant while planning a surgical procedure and must be taken into account in order to prevent injuries to neurovascular structures and avoid serious hematoma.

The aim of this study was to assess the location and anatomical characteristics of LF using CBCT.

Methods

The research was designed as a retrospective study in which 168 CBCT scans were analyzed. The CBCT images were made in the X-ray room of the Institute of Dentistry at the Faculty of Medical Sciences of the University of Kragujevac, Serbia. All scans of patients were made for diagnostic purposes. This research was approved by the Ethical Committee of the Faculty of Medical Sciences, University of Kragujevac, Serbia (No. 01-11060, from November 23, 2020).

The patients' images were made using The Orthophos XG 3D (Sirona Dental Systems GmbH, Bensheim, Germany) device (field of view 8 × 8 cm; isotropic voxel size 0.2 and 0.1 mm). The GALAXIS Software v1.9.4 (Sirona Dental Systems GmbH, Bensheim, Germany) was used for the three-dimensional reconstruction of images (image definition 100 μm). The patients' images were analyzed under standardized conditions in a room with diminished light on a Philips LED monitor (23 inches, 1,920 × 1,080 pixels).

The inclusion criteria in this study were the images of patients aged above 18 and the complete visibility of the mandible in the CBCT image. The scans that were not examined were those in which pathological lesions in the mandible, impacted teeth, and the presence of various deformities were noticed, as well as those with an incompletely visible mandible. Based on the mentioned criteria, 99 CBCT scans out of a total of 168 were taken for final data processing.

Two investigators, one oral surgeon and one dentist, with more than five years of experience in clinical practice, evaluated the LF. Software built-in meter was used to take all the measurements, and data were entered into an Excel table. All the measurements were repeated twice in 7-day intervals to ensure the objectivity of the measurement. The average value of the two recordings was used in the final data analysis in a situation where the measurement data differed.

In these scans, the presence of LF, the number of LF, and their location concerning the teeth and the mandibular region (Figure 1) (MLF – in the mandibular midline or near it; LLF – molar and premolar region) were analyzed. In addition, analysing the general anatomical characteristics was done (Figure 2), such as foramen diameter (≤ 1 mm – lower risk of hemorrhage; > 1 mm – higher risk of hemorrhage), the distance from the alveolar ridge crest, the distance from the inferior border of the mandible, the distance from the tooth apex and the position in relation to the tooth apex (above the apex; below the apex).

Software SPSS 18.0 (IBM SPSS Statistics 18) was used for statistical data processing. The mean values and the standard deviation of examined parameters, as well as descriptive statistics, were calculated. The Chi-squared test, Mann-Whitney *U* test, and independent samples *t*-test were applied to data analysis.

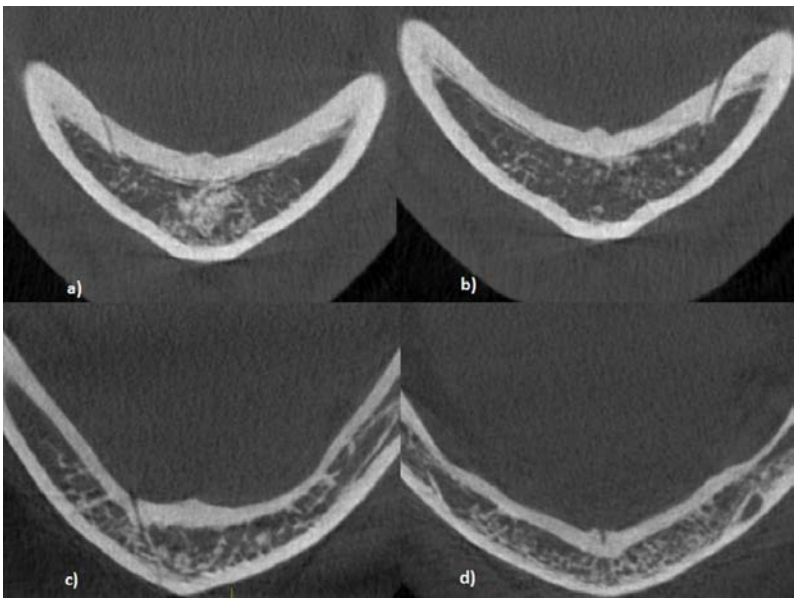

Fig. 1 – Display of lingual foramen (LF) position relative to mandibular region in axial view: a) and b) lateral LF; c) and d) median LF.

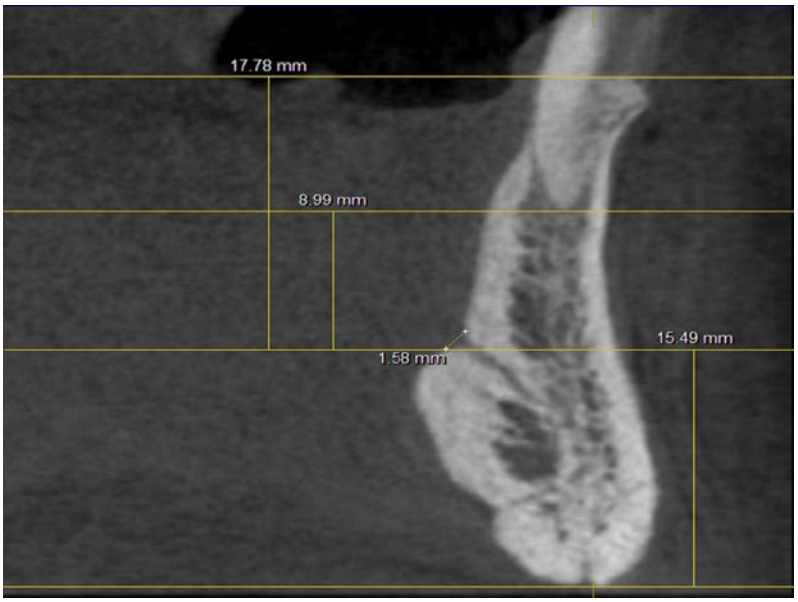

Fig. 2 – Display of diameter, the distance from the alveolar ridge crest and inferior border of the mandible, and the distance from the tooth apex to the lingual foramen in a cross-sectional view.

Results

In this study, the average age of the patients was 43.8 ± 16.2 (age range 19–84). Out of the total number of patients, 50.5% were male, whereas 49.5% were female. The analysis of 99 CBCT scans identified 234 LF. LF was detected in all patients. The number of LF *per* patient ranged from 1 to 6. The average frequency of LF *per* patient was 2.4 ± 1.2. In the largest number of cases, 42.4% of patients had 2 LF each, whereas only 2% of patients had 5 or 6 LF each. There is no statistically significant difference in the number of LF in relation to gender ($p = 0.956$) (Table 1).

By analyzing the regional frequency, 82.5% of LF belonged to MLF, while 17.5% belonged to LLF (Figure 3). Moreover, 67.7% of patients had only MLF, while 32.3% of patients had both MLF and LLF. There is no statistically significant difference in the regional frequency of LF (MLF/MLF and LLF) in relation to gender ($p = 0.558$) (Table 2). Concerning the tooth position, LF was mostly localized in the region of the lower central incisors, whereas they were least present in the region of the lower first molar (Figure 4).

In relation to the tooth apex, 98.3% of LF were localized below the tooth apex, while 1.7% were localized above the tooth apex. The average distance of LF from the tooth apex, for the LF localized above the tooth apex, was 2.8 ± 4.2 mm, whereas for the LF localized below the tooth apex, it was 10.8 ± 5.6 mm. There is no statistically signifi-

Table 1

Frequency of lingual foramen in relation to gender

Gender	Number of lingual foramen						Total
	one	two	three	four	five	six	
Male	12 (12.1)	23 (23.2)	6 (6.1)	7 (7.1)	1 (1.0)	1 (1.0)	50 (50.5)
Female	11 (11.1)	19 (19.2)	9 (9.1)	8 (8.1)	1 (1.0)	1 (1.0)	49 (49.5)
Total	23 (23.2)	42 (42.4)	15 (15.2)	15 (15.2)	2 (2.0)	2 (2.0)	100 (100.0)

All values are expressed as numbers (percentages).
Chi-Squared test $p = 0.956$.

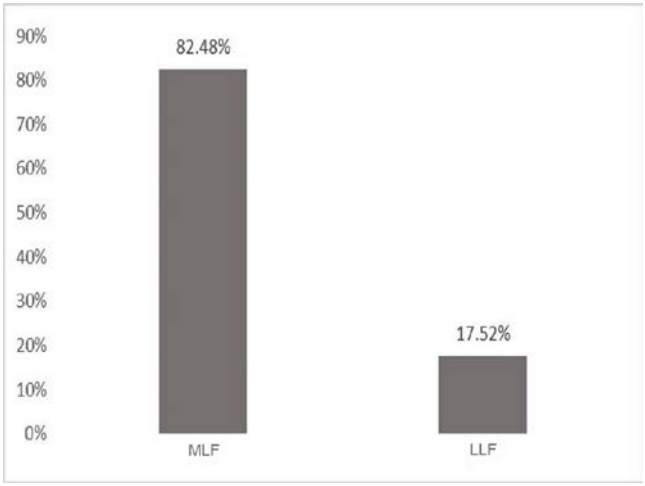

Fig. 3 – Graphical display of regional frequency of lingual foramen (LF).
MLF – median LF; LLF – lateral LF.

Table 2

Regional frequency of lingual foramen (LF) in relation to gender

Gender	Localization of LF		Total
	MLF	MLF and LLF	
Male	34 (34.3)	16 (16.2)	50 (50.5)
Female	33 (33.3)	16 (16.2)	49 (49.5)
Total	67 (67.7)	32 (32.3)	99 (100.0)

MLF – median LF; LLF – lateral LF. All values are expressed as numbers (percentages).
Chi-Squared test $p = 0.558$.

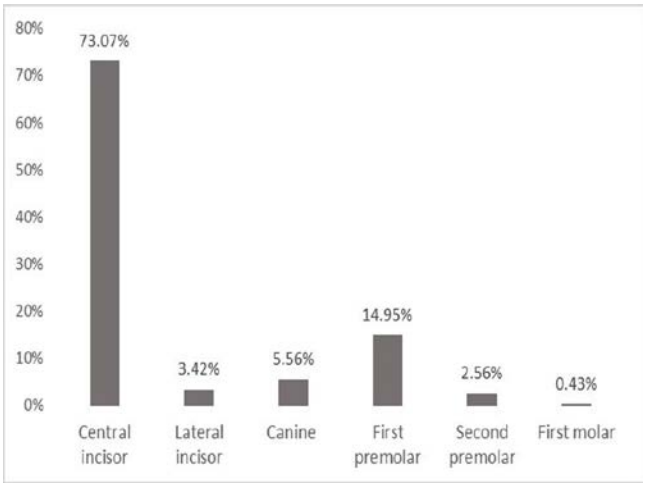

Fig. 4 – Graphical display of frequency of lingual foramen in relation to the tooth position.

cant difference in the localization of LF (above/below the tooth apex) in relation to gender ($p = 0.065$) (Table 3).

The average distance of LF from the alveolar ridge crest and the inferior border of the mandible, as well as the average diameter of LF in relation to gender, are presented in Table 4. There is a statistically significant difference in the distance of LF from the alveolar ridge crest and in the diameter of LF in relation to gender ($p = 0.019$; $p = 0.008$). There is no statistically significant difference in the distance of LF from the inferior border of the mandible in relation to gender ($p = 0.159$).

The average distance of LF from the alveolar ridge crest and the inferior border of the mandible, as well as the average diameter of LF in relation to the regional localization, are presented in Table 5. There is a statistically significant difference in the distance of LF from the alveolar ridge crest and the inferior border of the mandible in relation to the regional localization ($p = 0.000$; $p = 0.003$). There is no statistically significant difference in the diameter of LF in relation to the regional localization ($p = 0.059$).

In our study, 63.2% of LF had a diameter of ≤ 1 mm, whereas a diameter > 1 mm was recorded in 36.8% of LF (Figure 5).

Table 3

Frequency of lingual foramen above the apex or below the apex in relation to gender

Gender	Localization		Total
	above the tooth apex	below the tooth apex	
Male	0 (0.0)	115 (49.1)	115 (49.1)
Female	4 (1.7)	115 (49.1)	119 (50.9)
Total	4 (1.7)	230 (98.3)	234 (100.0)

All values are expressed as numbers (percentages).
Chi-Squared test $p = 0.065$.

Table 4

Distance of lingual foramen (LF) from the alveolar ridge crest, the inferior border of the mandible, and the diameter of LF in relation to gender

Gender	Average distance from the alveolar ridge crest	Average distance from the inferior border of the mandible	Average diameter
Male	21.8 ± 6.3	9.8 ± 5.5	1.0 ± 0.4
Female	19.9 ± 5.9	8.9 ± 5.2	0.9 ± 0.4
p	$^1p = 0.019$	$^2p = 0.159$	$^2p = 0.008$

All values are expressed in millimeter as mean value ± standard deviation.
[1] Independent samples t-test; [2] Mann-Whitney *U* test

Table 5

Distance of lingual foramen (LF) from the alveolar ridge crest, the inferior border of the mandible, and the diameter of LF in relation to the regional localization

Regional localization	Average distance from the alveolar ridge crest	Average distance from the inferior border of the mandible	Average diameter
MLF	20.2 ± 6.5	10.0 ± 5.6	0.9 ± 0.4
LLF	23.8 ± 3.4	6.5 ± 1.8	0.8 ± 0.2
p	$^1p = 0.000$	$^2p = 0.003$	$^2p = 0.059$

MLF – median LF; LLF – lateral LF. All values are expressed in milimmeter, as mean value ± standard deviation.
[1] Independent samples t-test; [2] Mann-Whitney *U* test

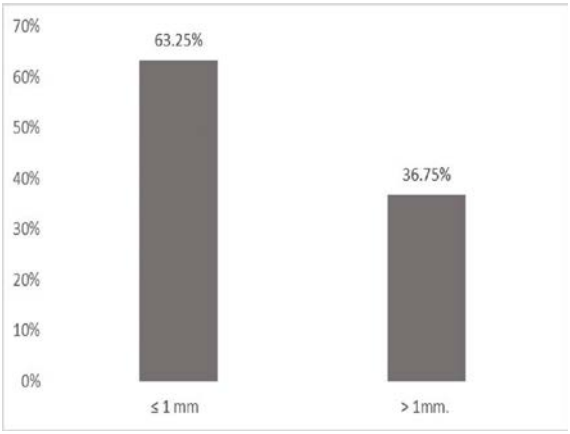

Fig. 5 – Graphical display of frequency of lingual foramen in relation to diameter.

Discussion

Numerous studies have described the presence of additional foramina on the inner side of the mandible without clear classification and nomenclature, pointing out their potential clinical importance [26, 27]. LF is often neglected while planning surgical procedures in the mandible, particularly in the anterior part of the mandible, which is regarded as a safe zone for the placement of implants [1, 6, 18].

The frequency of LF in our study is 100%, i.e., it was detected in all 99 patients. The systematic review and meta-analysis, which covered ten computed tomography studies of patients and cadavers, showed that the frequency of LF in the mandible ranged from 96.2% to 100% [28]. Furthermore, several similar studies, which covered the analysis of CBCT scans, showed a high frequency of LF, from 96.6% to 100% [2, 5, 7, 29]. Isman et al. [30] state that panoramic radiography can identify LF in the anterior part of the mandible in only 8 (4%) patients with certainty, whereas a high degree of probability for its existence was recorded in 25 (12.5%) patients. The use of CBCT results in obtaining cross-sections of high resolution and different thicknesses, which makes it superior to the other radiographic techniques for visualization of LF [31, 32].

In our study, the number of LF *per* patient ranged from 1 to 6. The largest number of patients had 2 LF each, whereas the smallest number of patients had 5 or 6 LF each. Such a result coincides with the results of the study conducted by Demiralp et al. [7]. However, Denny et al. [2] showed that the number of LF *per* patient ranged from 1 to 3. In the study by He et al. [1], most patients had 3 or 4 LF each, whereas the patients with 8 LF each were the least present. The differences noticed in the results of the studies probably come from different CBCT devices and software used in the visualization of mandibles, as well as from potential anatomical geographical differences in the mandible [1].

Out of the total number of analyzed LF, our study showed that 82.5% belong to the MLF type, whereas 17.5% belong to the LLF type. Likewise, LF was most frequently localized in the region of the lower central incisors, whereas it was least present in the region of the lower first molar. Such a result coincides with the results of the studies conducted by He et al. [1], Denny et al. [2], and Trost et al. [33], who showed that most of the total number of LF belonged to MLF. Only the study by Chirita et al. [34] presented that most of the total number of LF belonged to LLF. These results indicate that both the anterior and lateral regions of the mandible must be taken into account while planning oral surgery interventions because of possible complications due to the injury of the neurovascular bundle passing through LF.

In our study, LF was localized below the tooth apex in 98.3% of cases. Several previous investigations also showed that LF was mostly localized below the tooth apex [1, 34]. The average LF distance from our study's tooth apex is 10.8 ± 5.6 mm. A similar result was obtained in the study by Yildirim et al. [4], where the average distance of LF from the tooth apex is 10.1 ± 4.4 mm. Even though our study showed a high average distance of LF from the tooth apex, it is recommended that CBCT scanning be done before surgical procedures, particularly if the immediate placement of implants is planned [4]. Attention should also be paid to the LF located above the tooth apex, which is much more easily injured during endodontic surgery, especially if it is known that in our study, the average distance from the tooth apex is 2.8 ± 4.2 mm [1].

In our study, the average distance of LF from the alveolar ridge crest is somewhat higher in males, and it is 21.8 ± 6.3 mm, whereas in females, it is 19.9 ± 5.9 mm. Our study showed a statistically significant difference in the distance of LF from the alveolar ridge crest in relation to gender (p = 0.019). The study by Yildirim et al. [4] also showed a statistically significant difference in the distance of LF from the alveolar ridge crest in relation to gender (p = 0.000). The distance between LF and the alveolar ridge crest is clinically significant for surgical intervention because it can limit the length of the implant placed (especially in elderly patients) [1]. In our research, the average distance of LF from the inferior border of the mandible is somewhat smaller in females, and it is 8.9 ± 5.2 mm, whereas in males, it is 9.8 ± 5.5 mm. Our study showed that there is no statistically significant difference in the distance of LF from the inferior border of the mandible in relation to gender (p = 0.159), which coincides with the results of the study by Wang et al. [6] (p = 0.220). Moreover, in our study, the average diameter of LF is more pronounced in males, and it is 1.0 ± 0.4 mm, whereas, in females, it is 0.9 ± 0. 4 mm. In contrast to our study (p = 0.008), the study by Trost et al. [33] (p = 0.106) showed no statistically significant difference in the diameter of LF in relation to gender.

By analyzing the regional localization, our study showed a statistically significant difference in the distance of LF from the alveolar ridge crest and the inferior border of the mandible in relation to the regional localization (p = 0.000; p = 0.003). In our study, the average distance between MLF and the alveolar ridge crest was 20.2 ± 6.5 mm, while the average distance between LLF and the alveolar ridge crest was higher, i.e., it was 23.8 ± 3.4 mm. However, in the study by Yildirim et al. [4], the distances of MLF and LLF from the alveolar ridge crest are approximately equal (MLF: 18.2 ± 5.8 mm; LLF: 18.4 ± 5.1 mm). The differences in distance are probably the consequence of anatomical variations and ethnicity [11]. A shorter distance of LF from the alveolar ridge crest increases the risk of injury of the neurovascular bundle during surgical procedures, particularly in the anterior part of the mandible. With atrophy, the height of the edentulous ridge decreases, and the crest approaches the LF, thus putting the vascular bundle in peril of being cut by an implant drill. The distance from the LF to the residual ridge was ~7 mm less in edentulous patients compared to dentulous patients. In patients with alveolar ridge atrophy, shorter implants can reduce the risk of undesired incidents [33]. In our study, the average distance between MLF and the inferior border of the mandible is 10.0 ± 5.6 mm, whereas the average distance between LLF and the inferior border of the mandible is smaller, i.e., 6.5 ± 1.8 mm. Likewise, in the study by Zhang et al. [22], the average distance between MLF

and the inferior border of the mandible is higher than the average distance between LLF and the inferior border of the mandible (MLF: 13.8 ± 2.2 mm; LLF: 7.0 ± 1.9 mm).

In our study, the average LF diameter values in relation to the regional localization were approximately equal (MLF: 0.9 ± 0.4 mm; LLF: 0.8 ± 0.2 mm). Furthermore, in the research by Zhang et al. [22], the average values of the diameter of LF in relation to the regional localization were approximately equal (MLF: 0.7 ± 0.2 mm; LLF: 0.6 ± 0.2 mm). In contrast to our study, where there was no statistically significant difference in the diameter of LF in relation to the regional localization ($p = 0.059$), the study by Yildirim et al. [4] showed that the diameter of MLF was larger than the diameter of LLF ($p = 0.002$). LF with larger diameters may have a negative influence on the osseointegration of implants, i.e., they may be involved in postoperative sensory disturbances and serious hematoma [1]. The diameter of LF influences the degree of risk of hemorrhage. In the previous studies, the risk of hemorrhage was established based on the diameter of LF (≤ 1 mm – lower risk of hemorrhage; > 1 mm – higher risk of hemorrhage). Our research showed that 63.2% of LF have a diameter ≤ 1 mm, whereas 36.8% have a diameter > 1 mm. Several similar investigations also showed that LF had a diameter ≤ 1 mm [1, 4, 6, 7] in most cases. However, in the study by Trost et al. [33], most LF had a diameter > 1 mm. Knowing that there is a higher risk of hemorrhage in the arteries whose diameter is ≥ 1 mm, it is necessary to preoperatively assess the risk of hemorrhage if the radiological analysis detects that the diameter of LF is > 1 mm [3, 35].

Conclusion

The results of this study indicate variability in the location and anatomical characteristics of LF, which is confirmed by other studies. LF can be reliably localized and visualized using CBCT scanning because there is no superimposition of the anatomical structures, better contrast resolution, and fewer or no artifacts. To prevent operative complications such as the possibility of injury of the neurovascular bundle which passes through it, particular attention should be paid to the distance from the alveolar ridge crest in women (especially in elderly patients) and to the distance from the alveolar ridge crest in relation to the regional localization (especially in MLF).

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Correlation of the radial inclination angle in the distal part of the radius with the volar cortical angle and age-related changes of these angles

Korelacija ugla radijalne inklinacije sa volarnim kortikalnim uglom i promene tih uglova sa starenjem

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Abstract

Background/Aim. The radial inclination (RI) and volar cortical (VC) angle values used in the treatment of radial distal end fractures may vary depending on factors such as the age and gender of the patient. That raises the question of the compatibility of the standard anatomical plates, which are frequently used in the surgical treatment of these fractures. The aim of the study was to evaluate the VC and RI angles depending on the age and gender of subjects and determine the correlation between these two angles. **Methods.** A total of 121 individuals (59 females and 62 males) aged 10–65 years were included in the study. The individuals were divided into two groups: a group of 60 adolescents (31 females, 29 males) 10–20 years old and a group of 61 adults (28 females, 33 males) aged 20–65 years. The subjects were also evaluated between themselves, independently, within each age group. Radiographic images were evaluated by using the 3.0.1.55 version of the KarPacsViewer application. Measurement points were determined, and angles between these points were measured. Statistical analyses were made using the SPSS 15.0 program. **Results.** When the correlation for 121 individuals was assessed independently of their gender, no statistically significant relationship was found between the RI angle and age ($p = 0.616$; $r = -0.046$). A statistically negative (or opposite) relationship was found between the VC angle and age ($p < 0.001$; $r = -0.396$). When women and men were compared in terms of the RI and VC angles, no statistically significant difference was found ($p = 0.958$, $p = 0.165$, respectively). The VC angle decreased as the age increased in females ($p = 0.004$; $r = -0.365$), while both the RI and VC angles decreased with increasing age in males ($p = 0.032$, $r = -0.273$; $p < 0.0001$, $r = -0.445$, respectively). **Conclusion.** Our findings regarding the RI and VC angles offer an advantage in terms of determining which plate designs are most appropriate for planning surgical procedures and treatment processes.

Key words:
age factors; bone plates; radiography; radius fractures; weights and measures.

Apstrakt

Uvod/Cilj. Vrednosti radijalne inklinacije (RI) i volarnog kortikalnog (VK) ugla, parametri koji se koriste u lečenju preloma distalnog okrajka žbice, mogu varirati zavisno od faktora kao što su godine i pol pacijenta. To dovodi u pitanje kompatibilnost standardnih anatomskih ploča, koje se često koriste u hirurškom lečenju tih fraktura. Cilj rada bio je da se procene uglovi VK i RI, u zavisnosti od starosti i pola ispitanika, kao i da se utvrdi korelacija između ta dva ugla. **Metode.** U studiju je bilo uključeno ukupno 121 osoba (59 žena i 62 muškarca) starosti od 10 do 65 godina, podeljenih u dve grupe: grupa od 60 adolescentnih ispitanika (31 žena, 29 muškaraca) starosti od 10–20 godina i grupa u kojoj je bilo 61 odraslih osoba (28 žena, 33 muškarca) starosti od 20–65 godina. Takođe, sprovedene su i nezavisne procene između pojedinaca unutar svake pojedinačne grupe. Radiografske slike procenjene su uz pomoć 3.0.1.55 verzije aplikacije *KarPacsViewer*. Određene su merne tačke i izmereni uglovi između tih tačaka. Statističke analize rađene su pomoću programa SPSS 15.0. **Rezultati.** Kada je korelacija kod svih 121 ispitanika određivana nezavisno od njihovog pola, nije pronađena statistički značajna veza između ugla RI i starosti ispitanika ($p = 0{,}616$; $r = -0{,}046$). Nađen je statistički negativan (ili suprotan) odnos između ugla VK i starosti osoba

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($p < 0,001$; $r = -0,396$). Kada su žene i muškarci upoređivani u odnosu na vrednosti uglova RI i VK, nije utvrđena statistički značajna razlika ($p = 0,958$, $p = 0,165$, redom). Ugao VK je opadao sa porastom starosti žena ($p = 0,004$; $r = -0,365$), dok su uglovi RI i VK opadali sa porastom starosti muškaraca ($p = 0,032$, $r = -0,273$; $p < 0,0001$, $r = -0,445$, redom). **Zaključak.** Naši nalazi procene uglova RI i VK pružaju prednost kod izbora najprikladnijeg dizajna anatomskih ploča, onog koji najviše odgovara za planirane hirurške procedure i proces lečenja.

Ključne reči:
životno doba, faktor; pločice za kost; radiografija; radijus, prelomi; mere i merenja.

Introduction

Wrist movements are the actions we actively use in everyday situations, such as eating, drinking, using phones, and reading books. Any restriction that may occur on the wrist will negatively impact our daily life. During wrist-related movements, there is harmony between the bone, tendon, joint surface, and soft tissues. Wrist kinematics are examined under radiocarpal, carpal, and distal radioulnar joints [1, 2].

Five to ten percent of fractures in the skeletal system occur in the forearm. About 75% of these fractures were found to be distal radius fractures (DRF). Those who apply to the emergency department for DRF constitute 1/6 of all fracture applications. Twenty percent of DRF consist of unstable fractures and require surgical procedures. Fractures occur during high falls, motor vehicle accidents, or athletic activities at young ages. In elderly individuals, even the simpler falls may result in fractures [3–5].

The classification of fractures has a high impact on the treatment process today. This classification allows applying a treatment plan according to the fracture type and describing the relationship with soft tissue lesions. It is essential to have a good determination of the type of fracture and the level of injury. Thus, the treatment will be easier, and the recovery process will be accelerated. Colles fracture, Smith fracture, Barton fracture, Die-punch fracture, and Chauffeur's fracture are some of the DRF types [6].

Clinical and radiological findings of patients who applied to the hospital with wrist complaints are preliminary for treatment procedures. Direct radiography of DRF is the first step in evaluation. The initial assessment of direct radiographic images should include at least two radiographs – anteroposterior (AP) and lateral images. Oblique radiographs are also recommended for better visualization of various fracture lines. The long axis of the radius is used as the primary axis in all parameters used in the treatment and radiological follow-up of the fracture in the taken radiographs. Two of these parameters are radial inclination (RI) angle and volar cortical (VC) angle [7–9].

The RI angle is the angle between the tip of the styloid process and the vertical line drawn on the radius from the radial part of the distal radioulnar joint on the AP graph [10, 11]. The VC angle is the angle between the volar line drawn on the distal radius shaft and the line drawn to the distal metaphysis of the distal radius in the volar direction [12–14].

Volar plates aim to provide constant fixation in surgical procedures and are designed to reflect the natural anatomy. In certain DRF, the plates should fit anatomically on the volar surface of the distal radius. However, personal factors should be considered in the treatment planning of DRF, as well as clinical and radiological data. Factors such as age, gender, physical and cognitive condition, patient occupation, and open or closed fracture type are also important in planning treatment [15, 16]. Based on these specified factors, it is predicted that there may be changes in the anatomical VC angle according to age and gender. That has brought the discussion of how compatible standard anatomical plates will be.

In this study, we investigated the VC and RI angles depending on age and gender and the correlation between these two angles. That will allow preferring a suitable plate for the individual's anatomy during surgical procedures.

Methods

The research was carried out at the Adıyaman Provincial Health Directorate, Adıyaman Training and Research Hospital, and the Department of Orthopedics and Traumatology, Turkey. Our study was carried out by examining the records of patients who came to the Department of Orthopedics and Traumatology between January 1, 2015, and September 1, 2019. Ethical Approval (No. 2019/6-13, from September 17, 2019) was given by the decision of The Ethics Committee of Adıyaman University Faculty of Medicine.

Characteristics of the study groups

This study covers X-ray images of 121 adolescents and adults between the ages of 10 and 65 years who were admitted to the hospital between the specified dates and reported as healthy from patient records. Individuals with anatomical deformities in the distal radius due to traumatic, congenital, rheumatic, and similar conditions and those who had undergone surgical procedures on the distal radius were not included in the study.

The patients in this study were divided into two groups, a group of 60 adolescents (31 females, 29 males) under the age of 20 and 61 adults (28 females, 33 males) aged 20 and above. The 10–19 and 20–65 age groups were frequently used in previous wrist radiology studies. These age ranges were chosen in order to be compared with previous data [17–19]. In this study, two independent sample *t*-test procedures of the G*power (version 3.1.9.2) software were used to calculate the sample sizes of the groups by power analysis. The impact size was 0.85, targeted power 0.90, and significance level of 0.05 were considered bidirectional.

Radiographic evaluations

Wrist evaluation of patients was made with SG Healthcare Jumong U brand digital X-ray imagining system. In AP X-ray examination, the shoulder is positioned at 90° abduction, and the elbow is at shoulder level and 90° flexion. The palm is then placed on the X-ray machine. This position is the neutral supination-pronation state of the forearm. In lateral radiography, the patient is seated so that the forearm and hand are at the same level on the table. The shoulder is positioned at 0° abduction. The elbow is flexed 90°. The plane of the palm and the axis through the epicondyles of the humerus should be perpendicular to the table. The forearm should be in a fully lateral position. The wrist is placed sideways on the table so that the radius and ulna overlap and are superposed [20].

Measurement tools and techniques

One hundred and twenty-one patients with forearm and wrist complaints, who had not experienced any wrist trauma or surgical procedures, applied to the Department of Orthopedics and Traumatology of the Adıyaman Training and Research Hospital. The radiographs of these patients were taken by the standard radiographic imag-ing technique. The relevant points were marked, and measurement points were assigned with the 3.0.1.55 version of the KarPacsViewer application. Then, the distance between the determined points was measured with the aid of the application. The VC angle was obtained from lateral radiographs: a – straight line drawn along the volar surface of the shaft of the distal radius; b – the line following the anterior cortex of the distal end of the radius; c – VC angle (Figure 1). The RI angle was obtained from AP radiographs: x – the axis along the radius shaft; y – the line drawn between the radius styloid tip and the ulnar border of the distal radius; z – the line perpendicular to the radius shaft; v – RI angle (Figure 2).

Statistical analysis

Statistical analyses were made using the SPSS 15.0 program. The suitability of quantitative variables to normal distribution was evaluated with the single sample Kolmogorov-Smirnov test. An independent two-sample *t*-test was used in the comparison of two independent groups. Results are given as mean ± standard deviation (SD). Linear regression analysis and Pearson correlation status were evaluated for predictions and associations between age and anatomical measurements. The results of the categorical variables were given as frequency and percentage. The significance level was accepted as at least $p < 0.05$. The *r* value indicates the correlation coefficient. The strength of the correlation was determined by the *r* value close to 1 or -1. The strength of correlation was determined according to Quinnipiac University [21].

Results

The RI angle was 23.31° in women and 23.27° in men. The VC angle was 160.10° for women and 158.43° in men. When women and men were compared in terms of VC angles, no statistically significant difference was found ($p = 0.958$, $p = 0.165$, respectively).

When the results were assessed according to gender, there was no statistically significant relationship between RI angle and age in women (n = 59) ($p = 0.301$; $r = 0.137$), while a significant relationship and moderate correlation coefficient were found between the VC angle and age; it was also

Fig. 1 – Volar cortical angle was obtained from lateral radiographs: a – straight line drawn along the volar surface of the shaft of the distal radius; b – the line following the anterior cortex of the distal end of the radius; c – volar cortical angle.

Fig. 2 – Radial inclination angle was obtained from anteroposterior radiographs: x – the axis along the radius shaft; y – the line drawn between the radius styloid tip and the ulnar border of the distal radius; z – the line perpendicular to the radius shaft; v – radial inclination angle.

observed that as age increased, the VC angle was decreasing (p = 0.004; r = -0.365) in women. However, there was no statistically significant relationship between the RI and VC angles (p = 0.854; r = 0.024). In males (n = 62), it was observed that both RI and VC angles decreased significantly as the age increased, and the correlation coefficient was strong (p = 0.032, r = -0.273; p < 0.0001, r = -0.445, respectively). However, no statistically significant relationship was found between RI and VC angles (p = 0.873; r = -0.021) (Table 1).

A comparison of the RI and VC angle features by age groups was made in men and women. There was no significant difference in the RI angle among the age groups in women (p = 0.334). In terms of the VC angle, a significant difference was found in age groups (p = 0.005). The RI and VC angle values of the 10–19 age group in males were significantly higher than in the 20–65 age group (p = 0.018, p = 0.0001, respectively). When the angle values of the RI and VC angle properties were examined according to gender groups by making age distinction, it was determined that both the RI and VC angle values did not differ according to gender between the ages of 10–19 years (p = 0.119, p = 0.858, respectively). Similarly, in the 20–65 years age range, it was determined that both the RI and VC angle values did not differ according to gender (p = 0.099, p = 0.077, respectively) (Table 2).

When the regression analysis graph of the angle values between the ages of 10–19 years was evaluated, there was no significant increase or decrease in RI angle with increasing age in this age range (p = 0.753). Angle change was independent of the 10–19 years age range (Figure 3).

When the regression analysis graph of the VC angle values between the ages of 10–19 years was evaluated, the VC angle showed a change with age. There was a significant decrease in VC angle as age increased in the 10–19 years age range (p = 0.012). The correlation coefficient strength was moderate (r = 0.32) (Figure 4).

In Figure 5, the regression analysis graph of the RI angle values between the ages of 20–65 years is given. In this age range, there was no significant increase or decrease in the RI with increasing age (p = 0.868). The RI angle change was independent of the age range of 20–65 years.

In Figure 6, the regression graph of the VC angle values for subjects in the 20–65 years group is given. In this age range, there was no significant increase or decrease in VC angle with increasing age (p = 0.981). VC angle change was independent of the age range of 20–65 years.

Table 1

Relationship of radial inclination (RI) and volar cortical (VC) angles with age and gender

Gender	RI angle	VC angle	Age
Women (n = 59)			
RI angle			
Pearson correlation	1	0.024	0.137
p-value		0.854	0.301
VC angle			
Pearson correlation	0.024	1	-0.365
p-value	0.854		0.004
Men (n = 62)			
RI angle			
Pearson correlation	1	-0.021	-0.273
p-value		0.873	0.032
VC angle			
Pearson correlation	-0.021	1	-0.445
p-value	0.873		< 0.001

Pearson correlation test was applied.

Table 2

Comparison of radial inclination (RI) and volar cortical (VC) angle features by age groups and gender

Parameter	Gender	n	Mean ± SD	*p*-value*	
				gender (w/m)	age groups, yeras (10–19/20–65)
Age 10–19 years					
RI angle	w	31	22.81 ± 4.42	0.119	0.334
	m	29	24.40 ± 3.19		
VC angle	w	31	162.29 ± 5.23	0.858	0.005
	m	29	162.54 ± 5.54		
Age 20–65 years					
RI angle	w	28	23.85 ± 3.71	0.099	0.018
	m	33	22.28 ± 3.61		
VC angle	w	28	157.69 ± 6.85	0.077	< 0.001
	33	33	154.82 ± 5.62		

w – women; m – men; n – number; SD – standard deviation.
*** – two independent sample *t*-tests were used.**

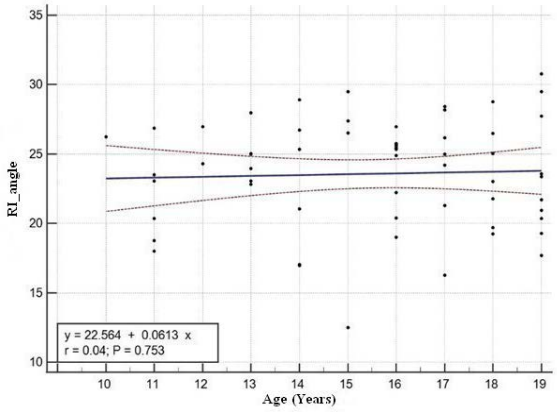

Fig. 3 – Regression analysis graph of the radial inclination angle in the 10–20 years age group.

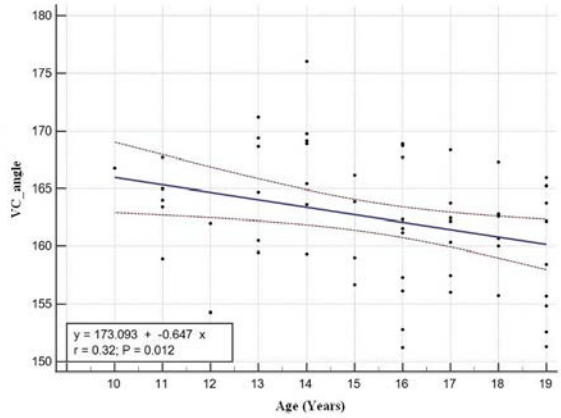

Fig. 4 – Regression analysis graph of the volar cortical angle in the 10–20 years age group.

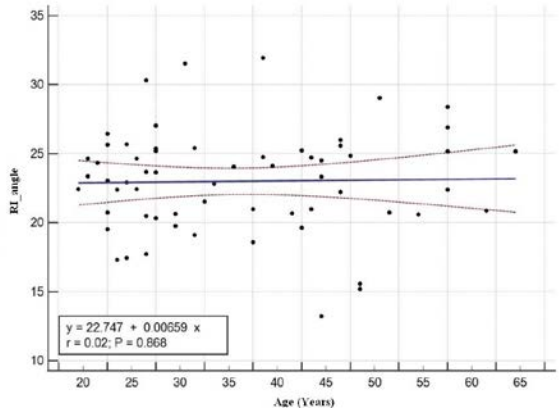

Fig. 5 – Regression analysis graph of radiation inclination angle in the 20–65 years age group.

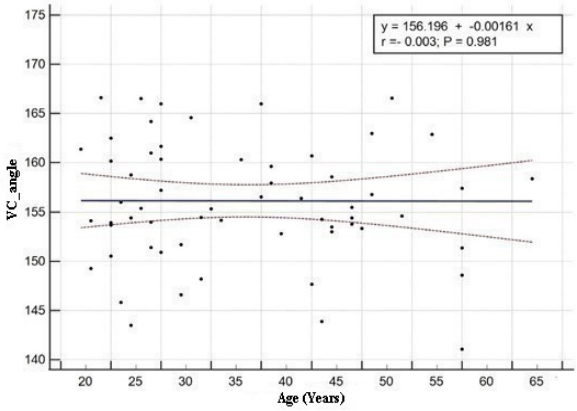

Fig. 6 – Regression analysis graph of volar cortical angle in the 20–65 years age group.

Discussion

The harmony between the bone, tendon, joint surfaces, and soft tissues is essential during hand and wrist-related movements. These structures are affected by fractures and injuries in bones [1, 2], and the VC angle is among the parameters used in the treatment and radiological follow-up of fractures [7–9]. Conservative or surgical operation procedures are performed on the fractures. Plating with volar and dorsal plates, fixation with an external fixator, and wiring with Kirschner wires are among the methods that can be encountered in surgical techniques. Today, fixed-angle anatomical plates are applied. However, since people may have anatomical variations, new techniques have been searched [22–25]. Gender and age factors are important values for us in plate applications. In addition, considering the age factor, the age group under 20 and the age group aged 20 and above should be considered as a category that should be evaluated. In light of this information, the correlation of the distal radius angle with the VC angle and age-related changes was investigated in our study. A few studies on this subject were found in the literature studies.

Namazi and Khaje [18] found the mean angle as 23.78° in individuals over 20 years of age on distal radius radiography images. No significant difference between men and women in any age group regarding mean variables was found. The results of this study and our study are similar. In our study, the angle was 23.31° in women and 23.27° in men. There was no significant difference between men and women in terms of angle. Ağır et al. [13] found that VC angles varied between 134.50 and 158.40. In our research, the VC angle was 160.10° in women and 158.43° in men. The variability of VC angles should be considered anatomically in fixed-angle locked volar plates.

Kwon et al. [26] investigated the harmony between anatomic plate designs and the morphometric variations of the distal radius in the volar direction. The findings of this study using computed tomography images showed that the results varied by race and gender. Kwak et al. [27] investigated the compatibility of volar-locked plates to the volar cortex of the distal radius, and VC angles of the radial and middle columns of the volar-locked plates were determined. The results were compared with the VC angles of the distal radius of 90 cadavers. Variability was observed in the columns and volar angles. As a result of these studies, it was predicted that the anatomic volar-locked plate should be chosen carefully, and a plate with appropriate angulation should be preferred for each patient.

Gandhi et al. [14] reported that the VC angle decreases with age. In addition, there was a difference between the

genders, and it was observed that the VC angle in men was wider than in women. They found the mean VC angle value greater in terms of the locked plates used. The conclusion of this study that the VC angle decreases with age is similar to the findings of our study. In this study, it was found that the VC angle in men was wider than in women. In contrast, our study showed no statistically significant difference in the values of VC angles in men and women.

Evans et al. [28] investigated the suitability of the VC angle to modern volar plate designs in their studies. The VC angle in men was found to be significantly higher than in females. However, no correlation was found between age and VC angle in the study. This study showed that the VC angle measured at the distal radius is significantly greater than the volar angulation incorporated in modern plate design. In our study, it was determined that VC values did not differ according to gender. Furthermore, in our study, a significant difference was found when the VC angle was compared in men and women according to age groups.

Gandhi et al. [14] reported that the VC angle decreased significantly between the ages of 20 and 80, regardless of gender. In our study, VC decreased significantly only in patients 10–19 years of age. No increase or decrease was observed in later age.

The present study has several limitations. In our study, we included adults from 20 to 65 years old as one of our groups. In order to conduct a more detailed study, it may be beneficial to focus on a specific age group within the range mentioned. Evaluating separately age groups such as 20–35, 35–50, and 50–65 years could provide more in-depth analysis. Therefore, further research is necessary to compare our results.

Conclusion

We believe that our findings regarding the RI and VC angles will offer an advantage in determining the appropriate plate designs and planning surgical procedures and treatment processes. We are also of the opinion that technological advances in medical devices should be followed and applied to patients within specific criteria.

Conflict of interest

The authors declare no conflict of interest.

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Bifurcation lesions in the context of a PCI CTO – insight from a Belgrade single-center CTO registry

Bifurkacije u kontekstu PKI HTO – uvid u registar HTO jednog centra u Beogradu

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Abstract

Background/Aim. Chronic total occlusions (CTOs) of the coronary artery are still one of the most complex procedures in the treatment of coronary arteries. If there is a bifurcation lesion within the CTO, it is certainly one of the biggest challenges for interventional cardiologists. **Methods.** We present a retrospective analysis of patients from our center who underwent percutaneous coronary intervention (PCI) with a bifurcation lesion within the CTO and a side branch with a diameter of 2 mm or more from January 2017 to December 2020. **Results.** Out of the total 216 patients in the four-year period, 38 (18%) had a bifurcation lesion within the CTO. The most common bifurcation lesions (50%) were on the left anterior descending artery, and the least frequent (21%) on the circumflex coronary artery. CTO recanalization was successful in 35 (92%) patients. The one-stent technique was used in 27 (77%) patients, while the two-stent technique was used in 8 (23%) patients. **Conclusion.** Bifurcation lesions in the context of PCI CTOs are a relatively common finding in coronary angiography and represent a special challenge for CTO operators. The provisional technique (one-stent technique) is the most common strategy for the treatment of bifurcation lesions in patients with CTO.

Key words:
coronary angiography; coronary occlusion; percutaneous coronary interventions; stents.

Apstrakt

Uvod/Cilj. Hronične totalne okluzije (HTO) koronarnih arterija su i dalje među najsloženijim procedurama u lečenju koronarnih arterija. Ukoliko postoji bifurkaciona lezija u sklopu HTO, to je jedan od najvećih izazova za interventne kardiologe. **Metode.** Prikazujemo restrospektivnu analizu bolesnika lečenih u našem centru, kojima je rađena perkutana koronarna intervencija (PKI) sa bifurkacionom lezijom unutar HTO i bočnom granom dijametra 2 mm ili više, od januara 2017. do decembra 2020. godine. **Rezultati.** Od ukupno 216 bolesnika lečenih u četvorogodišnjem periodu, 38 (18%) ih je imalo bifurkacionu leziju u sklopu HTO. Najčešće bifurkacione lezije (50%) bile su na prednjoj descendentnoj koronarnoj arteriji, a najređe (21%) na cirkumfleksnoj koronarnoj arteriji. Uspešna rekanalizacija HTO ostvarena je kod 35 (92%) bolesnika. Tehnika jednim stentom korišćena je kod 27 (77%) bolesnika, dok je tehnika sa dva stenta korišćena kod 8 (23%) bolesnika. **Zaključak.** Bifurkacione lezije u kontekstu PKI HTO su relativno čest nalaz na koronarografiji i predstavljaju poseban izazov za HTO operatore. *Provisional* tehnika (tehnika jednim stentom) najčešća je strategija lečenja bifurkacionih lezija i kod bolesnika sa HTO.

Ključne reči:
angiografija koronarnih arterija; koronarna okluzija; perkutana koronarna intervencija; stentovi.

Introduction

In the field of interventional cardiology, percutaneous interventions (PCI) of chronic total occlusions (CTOs) of the coronary artery are still the biggest challenge, with a still lower percentage of successful interventions compared to non-CTO lesions [1, 2]. Despite the complexity and certain risk that these interventions carry, there is great interest in PCI CTOs due to evidence that successful recanalization improves patient symptoms and prognosis as well as cardiac function [3–10]. Approximately 20% of all lesions treated with PCI are bifurcation lesions [11]. Bifurcation lesion, as part of a

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CTO, represents an additional challenge in a rather complex intervention. These lesions are challenging because they occur at the point where two arteries branch off. There is always a need to preserve the access and maintain the Thrombolysis in Myocardial Infarction (TIMI) 3 flow through the side branch. This perquisite can make it quite difficult to treat the occlusion and bifurcation simultaneously. Furthermore, the anatomy of the bifurcation can be complex, and the lesion itself may be long and heavily calcified, which can make it challenging to navigate a guide wire or other interventional devices through the occlusion. Overall, bifurcation lesions within CTOs require advanced technical skills, experience, and specialized equipment for effective treatment. In the available literature, there is a paucity of studies on bifurcation lesions within CTO regarding incidence, clinical, angiographic, and procedural data [12–15].

In this article, we present the clinical, angiographic, and procedural characteristics of patients with CTOs and bifurcation performed in our center over a four-year period.

Methods

From January 2017 to December 2020, in the Catheterization Laboratory of the University Clinical Center of Serbia, CTO recanalization was attempted by experienced CTO operators in 216 patients. The study was approved by the Ethical Committee of the University Clinical Center of Serbia (No. 30/4, from December 17, 2015).

CTO was defined as a coronary obstruction with TIMI flow grade 0 with an estimated duration of more than three months [15]. Bifurcation lesions were defined by the presence of a side branch (SB) within the CTO body or 5 mm of the proximal or distal cap of the CTO lesion, with a reference SB diameter of 2 mm or more. A successful procedure was defined when residual stenosis of less than 30% and TIMI 3 flow in both branches was achieved. Procedure time was measured from the engagement of the ostium with the guiding catheter to its removal. Procedure time, fluoroscopy time, and the amount of contrast were recorded by the X-ray technician at the end of the procedure.

All patients had a clinical indication for PCI CTO: stable angina with evidence of myocardial ischemia and/or myocardial viability in the akinetic zone of the occluded artery with a reference vessel size equal to or larger than 2.5 mm by visual estimation. Likewise, all patients were pretreated with dual antiplatelet therapy. The Japan-CTO (J-CTO) score is the most widely used score, and its introduction has created a scoring system that predicts not only successful wire passage and procedural efficiency but also technical success and even complications. It is the sum of the following five binary parameters: blunt proximal cap, calcification, bending > 45°, length of occluded segment > 20 mm, and previously failed PCI attempt. Each of these independent variables was assigned a value of 1 when present. The operator made the decision whether the recanalization was done with an antegrade or retrograde approach, as well as whether the bifurcation technique with one or two stents was used as part of the preparation for the intervention.

Results

From January 2017 to December 2020, out of the total of 216 patients with CTO in the registry, 38 (18%) of them (mean age 59.32 ± 9.9 years, men 76%) had a bifurcation lesion within the CTO (Figure 1).

Bifurcation lesions were most often seen in the left anterior descending (LAD) artery (50%), then in the right coronary artery (RCA), and least frequently in the circumflex (Cx) artery (21%). Patients and their angiographic characteristics are shown in Table 1.

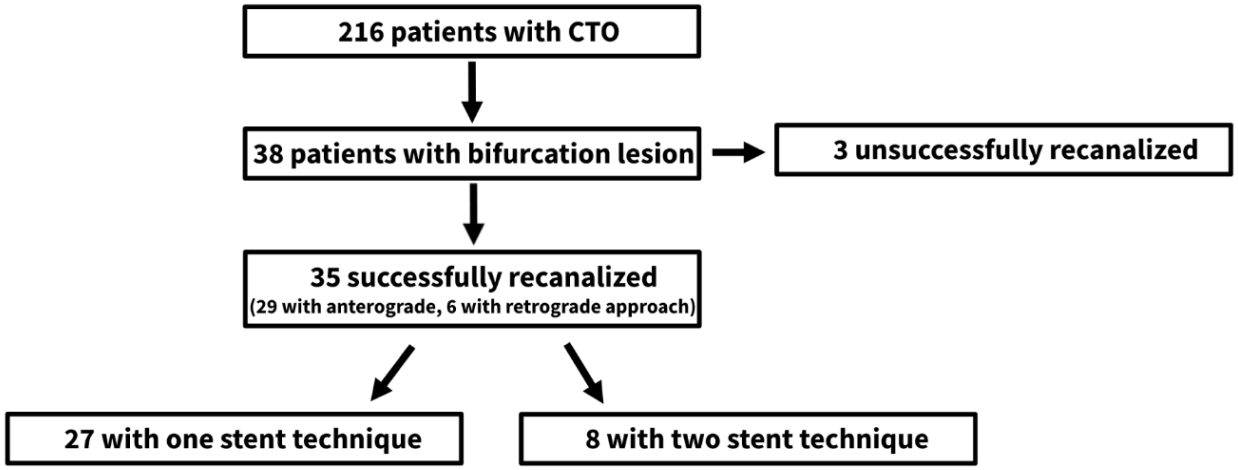

Fig. 1 – Chart flow of the patients.
CTO – chronic total occlusion.

Table 1

Patients with bifurcation lesion within the CTO (n = 38) and angiographic characteristics of those patients

Variable	Value
Age (years)	59.32 ± 9.9
Body mass index	27.2 ± 3.1
Baseline creatinine (mmol/L)	82.2 ± 15.9
Male	29 (76)
Female	9 (24)
Family history of CAD	19 (50)
Hypertension	31 (82)
Hypercholesterolemia	30 (79)
Diabetes mellitus	7 (18)
Ex-smoker	9 (24)
Current smoker	9 (24)
Previous stroke	0 (0)
Previous myocardial infarction	16 (42)
In-stent CTO	5 (13)
Angina	
CCS I	3 (8)
CCS II	28 (73)
CCS III	6 (16)
CCS IV	1 (3)
Reversible ischemia demonstrated	20 (53)
Presence of viability*	36 (95)
CTO artery	
LAD	19 (50)
Cx	8 (21)
RCA	11 (29)
Visual reference vessel diameter	2.99 ± 0.4
Visual length of occlusion	19.74 ± 8.5
Calcification	
none	4 (11)
mild	22 (58)
moderate	10 (26)
severe	2 (5)
Proximal cap tapered	27 (71)
Moderate/severe tortuosity	1 (3)
“Interventional” collateral present	23 (61)
J-CTO score	1.40 ± 1.17

Data are expressed as mean ± standard deviation or as numbers (percentages).

CAD – coronary artery disease; CTO – chronic total occlusion; CCS – Canadian Cardiovascular Society; LAD – left anterior descending; Cx – circumflex; RCA – right coronary artery; J-CTO – Japan CTO.

***Presence of viability: left ventricle (LV) normokinesis or segmental LV hypokinesis or documented viability in CTO territory.**

CTO with bifurcation lesion was successfully recanalized in 35 (92%) patients. Out of the total number of recanalized CTOs, successful recanalization by the anterograde approach was done in 29 (83%) patients, and by the retrograde approach in 6 (17%) patients. Specific CTO wires were used for all procedures, of which Fielder XT (n = 7; 20%), Gaia 1st (n = 5; 14%), Gaia 2nd (n = 12; 35%), Gaia 3rd (n = 6; 17%), Ultimate 3 (n = 3; 8%), or Conquest PRO (n = 2; 6%) were the wire which finally successfully crossed, with the support of microcatheters such as Corsair Pro (n = 13; 37%), Finecross (n = 17; 49%), Caravel (n = 3; 8%), or dual lumen microcatheter Sasuke (n = 2; 6%). In all successful recanalizations, new-generation drug-eluting stents were implanted. In addition to the standard one-stent technique (provisional technique), we often have to apply one of the techniques with two stents due to significant SB disease. The one-stent technique was used in 27 (77%) patients, while the two-stent technique was used in 8 (23%) patients. The two-stent technique is illustrated in Figure 2. The radial approach was used in 16 (42%) patients. Table 2 summarizes the procedural characteristics.

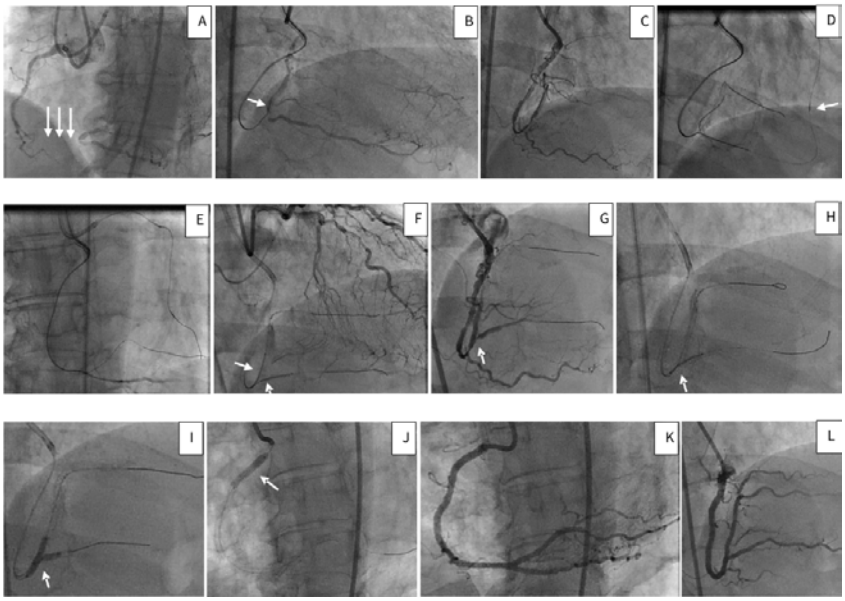

Fig. 2 – Application of the two-stent technique in a right coronary artery (RCA) chronic total occlusion (CTO) intervention with bifurcation lesion. A) Coronary angiography demonstrating a CTO of the distal RCA (arrow); B) A Gaia second™ guidewire (Asahi Intecc) was advanced into distal right posterolateral artery (arrow); C) Unsuccessful anterograde crossing attempt to the right posterior descending artery (PDA), after predilatation of the distal RCA, occlusion of the right PDA occured; D) The intervention continued with a retrograde approach, the Sion Black® guidewire (Asahi Intecc) passed the septal collaterals in the right PDA but neither the Corsair® Pro (Asahi Intecc) nor the Caravel® (Asahi Intecc) (arrow) could pass into the PDA; E) A Sion Black® guidewire was advanced from the crux to the PDA subintimally, but the geometry of the bifurcation was changed so that finally the Gaia Third™ guidewire (Asahi Intecc) with the support of Corsair passed antegrade into the right PDA into the right lumen; F) and G) The idea was to create a miniCrush (or modified T) bifurcation technique of the distal RCA; two stents (RCA-PL and ostium PD) were positioned (arrow), but it turned out that the ostium was not covered; H) Bail out was seen in the conversion to the culotte technique, with prior stenting of the distal right posterolateral artery and proximal optimisation technique of the distal RCA; I) Final kissing (arrow); J) Stenting of the proximal RCA was performed (arrow); K) and L) Final angiographic result showing successful recanalization of the RCA. PL – posterolateral (branch); PD – posterior descending.

Table 2

Procedural characteristics

Variable	Value
Radial approach	16 (42)
Contralateral injection	19 (50)
First guiding catheter 6fr	7 (18)
First guiding catheter 7fr	31 (82)
Microcatheter	35 (92)
Successful recanalization	35 (92)
anterograde recanalization	29 (83)
single wire	21 (60)
step up step down	8 (23)
retrograde recanalization	6 (17)
one-stent technique	27 (77)
two-stent technique	8 (23)
Total number of wires	2.6 ± 1.8
Total number of balloons	2.3 ± 0.8
Number of drug-eluting stent	1.9 ± 0.9
Total length of drug-eluting stent (mm)	50.7 ± 26.8
Maximal balloon diameter for postdilation (mm)	3.0 ± 0.6
Time of procedure (minutes)	84.4 ± 52.7
Fluoroscopy time (minutes)	33.4 ± 23.2
Contrast (mL)	297.3 ± 135.6
Patient dose (mGy)	1501.4 ± 138.3

Total number of patients = 38. Data are expressed as mean ± standard deviation or as numbers (percentages).

Discussion

In our study group, we analyzed the incidence of bifurcation lesions in CTO, as well as the clinical and angiographic data of patients from our center over a four-year period.

Several studies have evaluated the incidence of bifurcation lesions in the context of CTO lesions. In a series of 922 CTOs, Galassi et al. [13] had an incidence of 26.5% with a bifurcation lesion, while in a single-center prospective CTO registry, Chen et al. [16] and Ojeda et al. [12] had a higher incidence of bifurcation lesions (47% and 33%), which mostly depended on the adopted definition of bifurcations in CTOs. In their multicenter registry, with more than 900 CTO patients included, Ojeda et al. [14] demonstrated that 26% of them had a bifurcation lesion within the CTOs. In these few available CTO registries, we register higher rates of the presence of bifurcation lesions compared to the presence of the same lesions in PCI in the general population [11]. That can be explained by the fact that patients with CTO also have more aggressive atherosclerosis.

The registry of Ojeda et al. [14] showed, like our study, that the most frequent bifurcation within the CTOs was on the LAD.

In our group of patients, the majority of bifurcation lesions were treated with the one-stent technique. In the study by Ojeda et al. [12], about 93% of patients with a bifurcation lesion were treated with the one-stent technique. Chen et al. [16] had a slightly lower percentage (75%) of the one-stent technique in proximal bifurcation lesions, and our results are similar to theirs.

Our results are also in agreement with the results by Galassi et al. [13] as well as Ojeda et al. [14] that had procedural success at 87.3% and 85%, respectively, while in another study by Ojeda et al. [12], a slightly lower procedural success was observed.

When we talk about the complexity of the interventions themselves, as we said, the presence of a bifurcation lesion in the CTOs makes the operator's job even more difficult. Therefore, a J-CTO score of 1 or more is expected, which means a longer intervention time, fluoroscopy as well as radiation exposure. As shown in previous research conducted by Ojeda et al. [14], patients treated with a simple approach had average values of J-CTO score (1.8), fluoroscopy time (47.1 min), and contrast volume (about 326 mL), and our results are very similar to that data. The same data from the PROGRESS-CTO register [17], depending on the bifurcation site, speak in favor of a slightly longer intervention time (110–120 min) and radiation dose (2–2,500 mGy). Such data can be justified by more complex occlusions because the J-CTO score is somewhat higher (2.5–2.9).

Conclusion

Bifurcation lesions in the context of PCI CTOs are a relatively common finding in coronary angiography and represent a special challenge for CTO operators. The provisional technique (one-stent technique) is the most common strategy for the treatment of bifurcation lesions in patients with CTOs. With the advancement of technology as well as increasing experience in the field of CTOs, there is a high percentage of success in such complex PCI.

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Post-treatment periapical status related to the quality of root canal fillings in adults living in Vojvodina

Povezanost periapikalnog statusa zuba nakon lečenja sa kvalitetom punjenja kanala korena zuba kod odraslih osoba na području Vojvodine

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Abstract

Background/Aim. Apical periodontitis (AP) is an acute or chronic inflammation of the periradicular tissue, usually caused by the presence of microbial irritants in the root canal system. The aim of the study was to radiographically assess the AP prevalence in root-filled teeth (RFT) in adults from an urban area of Vojvodina, Serbia. **Methods**. Randomly selected digital ortopantomographs of 616 subjects who visited the Clinic of Dentistry of Vojvodina, from January 2019 to December 2020 were examined. Periapical status, root canal filling (RCF) quality, type of coronal restorations, and their relationships were evaluated. The Chi-squared (χ^2) test was used for statistical analysis. **Results.** The total number of endodontically treated teeth was 965; 44.25% of them received an adequate RCF score, and 34.9% had AP, which was diagnosed in 57.4% of inadequately scored RFT. Posterior teeth had significantly worse RCF quality than anterior teeth ($p < 0.001$). The direct logistic regression results indicated that a technically well-performed RCF reduced the risk of AP almost 21-fold. The prevalence of AP in our cohort was not influenced by the type of restoration (direct or indirect), but statistically significantly, the highest prevalence of AP was found in RFT without any coronal restoration. **Conclusion.** The results of this study reaffirm that technically high-quality root canal treatment is crucial to ensure a more predictable root canal treatment outcome.

Key words:
dental restoration, permanent; periapical periodontitis; radiography; serbia.

Apstrakt

Uvod/Cilj. Apikalni periodontitis (AP) je akutna ili hronična inflamacija tkiva oko vrha korena zuba (KZ), koja se najčešće javlja kao posledica prisustva mikrobioloških iritanasa u kanalnom sistemu KZ. Cilj rada bio je da se radiografski proceni učestalost AP na zubima koji su lečeni punjenjem kanala KZ (PKKZ) kod odraslih osoba iz urbanih područja Vojvodine, Srbija. **Metode**. Analizirano je 616 nasumično odabranih digitalnih ortopantomografa osoba, koje su posetile Kliniku za stomatologiju Vojvodine u periodu od januara 2019. do decembra 2020. godine. Ocenjen je periapikalni status, kvalitet PKKZ, tip nadoknade krunice zuba, kao i njihovi međusobni odnosi. Za statističke analize primenjen je χ^2 test. **Rezultati.** Ukupan broj endodontski lečenih zuba iznosio je 965, od kojih je 44,25% ocenjeno da poseduje adekvatno PKKZ, a 34,9% je imalo znake AP, koji je dijagnostikovan kod 57,4% zuba sa neadekvatnim PKKZ. Posteriorni zubi imali su značajno lošiji kvalitet PKKZ u odnosu na frontalne zube ($p < 0,001$). Direktnom logističkom regresijom je pokazano da je tehnički dobro izvedeno PKKZ smanjilo rizik od pojave AP skoro 21 put. Na učestalost pojave AP u našoj studiji nije uticao tip nadoknade (konzervativna ili protetska), ali je kod zuba sa PKKZ kojima nije rađena nadoknada krunice nađena statistički značajno viša učestalost AP. **Zaključak.** Rezultati ove studije su potvrdili da je visok tehnički kvalitet lečenja kanala KZ od ključnog značaja za predvidljiviji ishod terapije.

Ključne reči:
zub, trajni ispuni; periodontitis, periapikalni; radiografija; srbija.

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Introduction

The success of root canal treatment (RCT) depends on the prevention or complete healing of the periradicular tissue, usually caused by the presence of bacteria in the root canal system (RCS). Based on their comprehensive epidemiological study, Sjögren et al. [1] found that the expected RCT success rate for previously vital cases was 96%, whereas 86% of patients with infected RCS and chronic apical periodontitis (AP) showed signs of periradicular healing. Insufficiently cleaned and inadequately sealed areas of RCS can represent a reservoir of residual bacteria, inducing a constant stimulus that does not allow the AP healing process to begin.

As the RCT outcome is influenced by both clinician- and patient-related factors, clinicians should ensure the high technical quality of the root canal filling (RCF) as well as a long-lasting bond between the tooth structure and restorative material. By fulfilling these prerequisites, the risk of apical and coronal microleakage will be minimized, making the RCT outcome more predictable. Undoubtedly, even if all clinician-related factors are completely fulfilled, impaired inflammatory response (such as that seen in diabetes mellitus [2, 3]) might have an unfavorable impact on the final RCT outcome and should always be taken into consideration as an important prognostic aspect [4, 5].

However, there is presently no consensus on the relative importance of RCF and coronal restoration quality for RCT success, as some authors ascribe greater value to the coronal restoration quality [6, 7], while others emphasize the importance of the quality of the RCF, citing apical leakage as the main reason for endodontic failure [8, 9]. Still, it is widely accepted that apical termination for enlarging, shaping, cleaning, disinfecting, and filling should be at or within 2 mm of the radiographic apex [10]. Available evidence further suggests that an inadequate RCS disinfection due to missed canals [11] or other procedural errors, along with the low coronal or apical seal, is positively correlated with the poorer prognosis of endodontically treated teeth [12].

Moreover, AP is more commonly associated with root-filled teeth (RFT) than those that have not been subjected to RCT, but its prevalence in extant studies was highly variable and ranged from 24.5% to 61%. Thus, cross-sectional epidemiological studies are necessary for reliably assessing the burden of this disease in the general population and ascertaining if the applied RCT was successful [13, 14]. The observation of the prevalence of AP and its predisposing factors is gaining more and more importance and publicity, especially after gaining some knowledge about a possible connection with general health disorders [15, 16].

Considering the amount of useful data yielded by cross-sectional studies, the aim of the present study was to assess radiographically the AP prevalence and factors contributing to its occurrence in endodontically treated teeth, including apical RCF extension and coronal restoration type. These parameters were observed in adults treated at an urban dentistry clinic in Vojvodina, Serbia.

Methods

This cross-sectional study included randomly chosen ortopantomographs (OPGs) of 616 subjects; out of them, 265 (43%) were male and 351 (57%) were female, requiring full-mouth periapical radiographic examination as a part of the diagnostic and planning procedures at the Clinic of Dentistry of Vojvodina, seen between January 2019 and December 2020. The Ethics Committee of the Clinic of Dentistry approved the study (No. 01-16/61-2017, from November 23, 2017), and patient anonymity and data confidentiality were strictly respected. Periapical status and RCF quality were assessed during the examination of digital OPGs. To be eligible for participation, patients had to be between 18 and 70 years old and have fully readable OPGs. On the other hand, those with poor radiograph quality, as well as patients with fewer than nine natural teeth and/or teeth with root resection, were excluded. All teeth (except third molars) with radiopaque material in the root canals were considered endodontically treated. In every OPG, the patient's age and gender were recorded, along with the number of remaining teeth, the number and location of endodontically treated teeth, the technical quality of the RCF (length of root filling from the radiographic apex and its density), the type of coronal restoration placed on these teeth, and the presence/absence of AP signs and symptoms.

Digital OPGs were obtained using a Heliodent Vario D3350 (Sirona Dental Systems GmbH, Bensheim, Germany) and were automatically saved into the patient's electronic records. They were analyzed using Kodak Dental Imaging Software version 6.12.10.0-B for Windows (Carestream-Health, Inc. 2009).

Two endodontics specialists independently analyzed and scored only readable, clear radiographs in the darkroom using an illuminated viewing box and loupe. Their calibration was performed by double scoring 15 OPGs not included in the main study [17]. Inter-examiner agreement concerning the technical quality of RCF and the existence of apical radiolucency was evaluated by calculating Cohen's Kappa scores ($k = 0.82$).

The RCF was considered adequate when its tip was situated within 2 mm from the radiographic apex and was homogeneous without visible voids, with uniform radio-opacity across the entire length of RCS. Applied scoring was based on the European Society of Endodontology guidelines [18]. Multirooted teeth were scored according to the technical quality of the worst RCF and the most severe periapical status. If the canal was underfilled, poorly condensed, overfilled, with a separated file or any of the present canals was missed, the RCF was scored as inadequate.

In order to obtain results comparable to those yielded by similar cross-sectional studies, periapical tissues were assessed using the PeriApical Index (PAI score) developed by Orstavik et al. [19] whereby PAI 1 signified normal apical structures, PAI 2 denoted minor changes in bone structure, PAI 3 indicated changes in the bone structure with little mineral loss, PAI 4 was associated with periodontitis with a ra-

diolucent, well-defined area, and PAI 5 was assigned for severe periodontitis with aggravating features.

All data were processed and analyzed using SPSS, version 23.0 (Statistical Presentation System Software; SPSS Inc., Chicago, IL, USA). Statistical significance was assessed by the Chi-squared (χ^2) test and direct logistic regression was performed to calculate odds ratios (ORs) with 95% confidence intervals (CIs), whereby $p < 0.01$ was considered statistically significant. Finally, direct logistic regression was performed to assess the effect of the possible predictors of AP in RFT.

Results

The 616 OPGs used in the analyses featured 15,448 teeth in total, examined along with the associated periradicular tissues. The mean number of remaining teeth per subject in the overall sample was 25.08, while the mean of 25.11 was noted in female patients and 25.04 in male patients, with no significant differences between these groups ($p > 0.05$). The average values of the remaining teeth followed a downward trend in relation to patient age (Table 1).

The analyzed sample contained 965 RFT, corresponding to 6.25% of the overall number of teeth. Out of the total number of RFT, 44.25% received an adequate RCF score. Maxillary teeth were more frequently endodontically treated (69.7%) than teeth in the mandible (30.3%), and this difference was statistically significant ($p < 0.001$). Moreover, a significantly higher percentage of posterior teeth (65.6%) than frontal teeth (34.4%) had been endodontically treated ($p < 0.001$). The RCT was most prevalent in maxillary premolars (24.4%), and the lowest percentage was noted in mandibular canines (0.96%). Finally, 62.4% of female patients had RFT compared to 56.2% of male patients.

In the entire sample, only 427 (44.25%) teeth received an adequate RCF score. Moreover, 63.7% of posterior teeth had inadequately filled root canals, while in 40.7%, the technical quality of RCF in frontal teeth was statistically significantly superior ($p < 0.001$). The majority of RFT (420/538 or 78.1%) were assessed as inadequate due to short and inhomogeneous RCF in at least one of the root canals, and this issue was particularly prevalent in posterior teeth ($p < 0.001$). On the other hand, overfilling was detected in only 1.06% of RFT, and missed canals were noted in 10.4% of the examined cases. Canals were statistically significantly more likely to be missed in maxillary molars (63%) compared to lower molars (24%) ($p < 0.001$). File separation was noted only in posterior teeth, with an overall prevalence of 1.28% (Table 2).

AP (PAI ≥ 3) was noted in 507 (3.5%) of the examined teeth. While only 1.2% of non-RFT exhibited signs of AP, this percentage increased to 34.9% in RFT. In particular, 75.9% of posterior RFT were affected by AP compared to only 24.1% of frontal teeth, and this difference was statistically significant ($p < 0.001$). On the other hand, the prevalence of AP in RFT in the maxilla was comparable to that in the mandible (37.7% vs. 33.6%).

Periradicular pathosis was diagnosed in 309 (57.4%) of the 539 inadequate RFT while affecting only 8% of teeth in which RCF was assessed to be technically adequate. Moreover, 67.3% of short and/or homogenous RCFs were accompanied by radiographically visible resorptive changes in the periradicular area. Additionally, AP was observed in 78% of all RFT in which at least one canal was missed during treatment.

Indirect coronal restoration was performed on 313 (32.4%) RFT, and in 219 (70.2%) of those cases, periapical status was healthy. On the other hand, 581 (60.2%) teeth were directly restored coronally, and AP was evident in 33% of these cases. There were no statistically significant differences between the periapical status of teeth that had been indirectly coronally restored and those that had been directly restored ($p > 0.05$). Only 71 (7.4%) of RFT were not subjected to any restoration and exhibited statistically significantly the highest prevalence of AP (71.8%, $p < 0.001$), as shown in Table 3.

Table 1

Distribution of the number of remaining teeth according to patient's age and gender

Age group (years)	Patients (n)	Female/Male	Mean n of teeth (F/M)
18–29	184	112 (18.2)/72 (11.7)	29.5 (29.3/29.8)
30–39	184	102 (16.6)/82 (13.3)	26.04 (25.8/26.3)
40–49	135	75 (12.2)/60 (9.7)	22.5 (22.4/22.7)
50–59	70	39 (6.3)/31 (5.03)	20.5 (20.97/19.8)
≥ 60	43	23 (3.7)/20 (3.2)	17.5 (17.3/17.8)
Total	616	351 (57)/265 (43)	25.08 (25.1/25.04)

All values are expressed as numbers (percentages).
n – number; F – female; M – male.

Table 2

Distribution of technical quality of root canal filling according to the group of teeth

[1]Score	Group of teeth		*p*	Jaw		*p*
	frontal	posterior		mandibula	maxilla	
Adequate	197 (46.1)	230 (53.9)		121 (28.3)	306 (71.7)	< 0.001
Short/inhomogeneous	129 (30.7)	291 (69.3)	< 0.001	146 (34.8)	274 (65.2)	< 0.001
Missed canal	0 (0.0)	100 (100.0)	< 0.001	24 (24.0)	76 (76.0)	< 0.001
File separation/overfilled	6 (33.3)	12 (66.7)	< 0.001	1 (0.3)	17 (94.4)	< 0.001

All values are expressed as numbers (percentages).
[1] Score reflects the technical quality of root canal filling.

Table 3

Periapical status of root-filled teeth as a function of coronal restoration

Restoration type	Root-filled teeth	Root-filled teeth with AP	Root-filled teeth without AP
Direct	581 (60.2)	192 (33)	389 (67)
Indirect	313 (32.4)	94 (29.8)	219 (70.2)
Unrestored	71 (7.4)	51 (71.8*)	20 (28.2)
Total	965 (100)	337 (34.9)	628 (65.1)

AP – apical periodontitis. All values are expressed as numbers (percentages).
***Statistically significant $p < 0.001$.**

Table 4

Possible predictors of apical periodontitis in root-filled teeth

Parameter	B	SE	Wald	df	*p*	OR (95% CI)
Inadequately root-filled teeth	-3.034	0.230	174.448	1	< 0.001	20.8 (13.3–32.2)
Presence of any coronal restoration	-1.987	0.352	31.886	1	< 0.001	7.3 (3.66–14.49)
Constant	1.997	0.420	22.643	1	< 0.001	7.368

OR – odds ratio; CI – confidence interval; SE – standard error.

Based on the aforementioned findings, a model of RFT was developed based on the data from 965 examined cases. Even though the full model with tooth group, jaw, RCF score, and presence of coronal restoration included as four independent variables was statistically significant ($\chi^2 = 352.6$; $p < 0.001$), as shown in Table 4, only two predictors made a unique statistically significant contribution to its output. Based on the findings yielded by this more parsimonious model that excluded the tooth group and jaw, inadequate RCF increases the probability of AP in the root by 20.8-fold ($p < 0.001$; OR = 20.8; CI = 13.3−32.2). Additionally, the absence of coronal restoration increases the chance of AP by 7.3-fold ($p < 0.001$; OR = 7.3; CI = 3.66−14.49).

The *post-hoc* power analyses were conducted using G*Power 3.1.7.9. to estimate the achieved power of logistic regression analysis for two predictors with OR1 = 20.8 and OR2 = 7.3 on a sample of n = 965 and an alpha of 0.01. Results showed that the achieved power in both cases had a value of 1.

Discussion

Since one of the main goals of this study was to assess the AP prevalence, it was inevitably affected by the limitations commonly associated with all cross-sectional radiographic studies. In particular, as the time that elapsed between RCT, permanent restoration placement, and panoramic radiograph capture cannot be established, AP prevalence can be both under- and overestimated, as OPGs only provide a snapshot of patients' radiographic status. Although AP recorded on an OPG can be in a developing or healing phase, Petersson et al. [20] found that the number of healed and newly developed periapical lesions across a particular period was comparable. These findings prompted numerous cross-sectional studies based on radiograph analysis as a means of assessing AP prevalence within a particular population [21].

Additionally, the occurrence of clinical symptoms like pain, swelling, or sinus tract is a direct clinical indicator of RCT failure, which can be suspected when periapical lesion development or persistence in RFT is evident on the radiograph. According to Estrela et al. [22], a bone mineral loss of approximately 30–50% is required for lesions to be detected on conventional radiographs, which may lead to considerable AP underestimates when this approach is adopted. Similarly, although cone-beam computed tomography (CBCT) is more sensitive when adopted as an AP prevalence diagnostic tool, it leads to overestimates compared to histopathological analysis [23]. Furthermore, according to the most important recent recommendations, to limit radiation exposure, CBCT should be reserved for specific clinical cases rather than used for evaluation studies [24].

This study analyzed panoramic radiographs, which are not only more readily available and affordable but also expose patients to a lower radiation dose and allow all teeth to be displayed on a single radiograph [25]. Additionally, digital OPGs enable magnification of different areas in the panoramic radiograph as well as image enhancement to achieve better visualization of the region of RCS and periradicular tissue that is of particular interest. Still, despite the disadvantages related to the undesirable superimposition of anatomical structures, panoramic radiographs are useful for assessing the patient's overall dental health and detecting periapical lesions [26]. These observations are confirmed by the findings of a recent systematic literature review indicating that the majority of studies in this domain were based on panoramic radiographs, allowing their results to be compared and contrasted, which increases their external validity [27].

Given that the number of general dental practitioners in Serbia is significantly higher than the number of specialists, the majority of endodontic treatments examined in this study were likely performed by general practitioners. Consequently, RCT outcome is less likely to be successful, as rubber dam is rarely used in general dental practice, and there are also shortcomings in the cleaning process and shaping of RCS, as well as evidence of noncompliance with the irrigation protocol. Moreover, as this study was con-

ducted in only one state-funded clinical center, its findings cannot account for likely variations in the RCT outcome depending on the region of the country and the patent's income level. For instance, patients from rural areas tend to have fewer remaining natural teeth, and the RCF quality is typically lower than in urban settings. Therefore, the results reported here cannot be generalized to the entire adult population living in Vojvodina or the types of dental practice in which RCF is performed. Nevertheless, one of the main strengths of this study that can be highlighted, thanks to the size of the population sample, is that it provides a valuable overview of the general dental health of the observed population in a given period and shows that the prevalence of AP is one of the most important indicators of the outcome of RCT. Regarding this, obtained data may serve as important tools for further improvements in prevention and treatment plans for AP.

In the present study, the average number of remaining teeth per subject was 25.08, with a mean of 25.11 noted in females and 25.04 in males. These results are in line with the findings obtained in previous epidemiological studies conducted in Finland [28] and Greece [29] and are attributed to a relatively young patient age. Namely, more than half of our sample was aged below 40 and patients with fewer than nine remaining teeth (who probably lost most of their teeth owing to the periodontal disease) were excluded.

The prevalence of RFT (6.25%) in our sample was also comparable to that noted in studies carried out in Finland [28] and Spain [30]. Taking into account that the first mandibular molar is the first permanent tooth to erupt, it is not surprising that RCT is most frequently detected in mandibular molars [31]. In our study, 69.7% of all RFT were located in the maxilla, and posterior teeth were more likely to be endodontically treated compared to frontal teeth, concurring with previously reported results [29]. Furthermore, RCT was most likely to be performed in maxillary premolars, which coincides with the findings reported for the Austrian subpopulation [32].

Given that AP is a dynamic process, it is likely to be affected by RCT quality. Indeed, in our study, AP was detected more frequently in RFT (34.9%) than in non-RFT, and the same findings were reported by other authors [8], whereby 35% was reported for Thailand [33], 34.1% for Germany [34], and 31.5% for France [35]. Nonetheless, in previous studies, the prevalence of AP associated with RFT ranged from 24.5% to 61% [36], and this significant discrepancy likely arises due to differences in sample characteristics, OPG quality, and criteria applied for diagnosing AP.

The current study revealed that 55.8% of all RFT were inadequately obturated, concurring with 52.6% reported by Loftus et al. [17]. One of the main aims of this study was to establish the link between the low technical quality of RCT and periapical pathology, given that insufficient elimination of bacteria from RCS contributes to the AP development or persistence. In line with earlier findings, in our cohort, AP prevalence in posterior RFT was significantly higher compared to frontal RFT, likely due to the poorer technical quality of RCF in those groups of teeth owing to their more complex anatomy [25]. Therefore, it was not surprising that only 8% of technically adequate RFT were affected by AP, concurring with 7.3% reported for the Turkish population [36]. On the other hand, in the only previously published study involving the Serbian population, 25.9% of adequately scored RFT showed evidence of AP [37].

According to our model, the presence of AP was correlated significantly with inadequate RCF ($p < 0.01$). Indeed, 57.4% of the technically inadequate RFT (which comprised 55.7% of the sample) showed signs of AP, slightly exceeding 50.3% reported by Kielbassa et al. [32]. Inadequate root-filling length indicates insufficient canal disinfection and consequently increases the likelihood that AP will persist or develop. In this study, 67.3% of teeth with short and/or inhomogeneous RCF showed evidence of AP, in line with the previously published results [12, 38].

Missed canals during RCT in multirooted teeth usually indicate inadequate practitioner knowledge of tooth anatomy or complex canal configuration, which is conducive to bacterial proliferation, causing the development or maintenance of existing periapical lesions as a sign of treatment failure. In this study, 10.4% of all RFT had at least one missed canal, which is in line with the 12% reported by Baruwa et al. [39]. These authors also noted that canals were most likely to be missed in maxillary molars (59.5%), which supports our findings (63%). Similarly, both mesiobuccal root canals of maxillary molars were frequently missed during RCT, likely due to frequent deposition of tertiary dentin over their orifices, as a consequence of persistent untreated caries or the presence of deeper restorations, which significantly complicates the RCT procedure.

Unless there is a radiographically visible defect in the proximal surfaces, the quality of restoration, whether direct or indirect, can only be assessed when radiographs are interpreted alongside clinical findings. Thus, in this study, RFT were evaluated only if they were coronally restored, and the type of restoration was taken into consideration. According to Torabinejad et al. [40], bacterial colonization of root-filled canals without coronal restoration can be detected within three weeks. Our results also highlight the importance of coronal restoration as radiographic signs of AP were noted in 71.8% of teeth that had not been coronally restored. Moreover, in 23.5% of cases, AP was visible even though the technical quality of the RCF was adequate. Indirect restorations usually require the placement of temporary restoration material prior to its cementation in the next visit, which increases the possibility of coronal microleakage in the interim period. The major concern related to *post*-placement stems from the risk of perforation as well as poor cementation, which can also lead to microleakage [41]. On the other hand, placement of direct restorations, especially composites, carries the risk of gap formation on the gingival margins, which might provide an ideal path through which bacteria can access the root-filled canal, compromising the endodontic treatment success [42]. Still, it is worth noting that AP prevalence in our cohort was not affected by the restoration type (direct or indirect).

It should be emphasized that the strength of these cross-sectional studies is that they provide the information needed for the continuous improvement of dental education and subsequent dental practice. In this context, the present study can also be seen as a call for enhancing general dentists' knowledge and clinical skills, but also points to the need for referring patients to endodontics specialists when RCT needs to be performed on posterior teeth, especially molars. Finally, researchers must follow certain clearly defined guidelines for conducting cross-sectional studies so that results are more comparable. Recently, it was recommended that these guidelines be aligned with the developed checklist of Preferred Reporting points for Observational studies in Endodontics (PROBE 2023) [43] to improve the quality of these types of studies.

Conclusion

Despite the limitations of this study related to the possible underestimation of the real clinical situations, the yielded results indicate that well-performed RCF reduced the risk of AP by almost 21-fold, confirming its exceptional importance for RCT success.

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Practical analysis of the impact of social marketing strategies on attitudes of potential reproductive cell donors in the Republic of Serbia

Praktična analiza uticaja strategija socijalnog marketinga na stavove potencijalnih donora reproduktivnih ćelija u Republici Srbiji

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Abstract

Background/Aim. There is a constant increase in the need to use third-party reproductive cells among couples who are unable to conceive with their own reproductive cells or in order to prevent the passing of an existing hereditary genetic disorder to the child. The aim of the study was to present a theoretical overview and perform a practical analysis of the use of social marketing strategies using the first technique of analyzing the attitudes of potential donors of reproductive cells in the Republic of Serbia (RS) in the interest of adapting to the target group. **Methods.** Empirical research in this study, in which both women and men from the RS participated, was based on a questionnaire about people's willingness to be potential reproductive cell donors and about having information on the donation of reproductive cells. The data in this paper were obtained during 2021, and the questionnaire was focused on a particular population group. The questionnaire was sent to people aged 20 to 34 years who could become potential donors of reproductive cells. In the research, 201 women and men from the RS participated. The first part of the questionnaire was tested for internal consistency, which was tested by Cronbach's alpha coefficient calculation (α). Values of α lower than 0.5 indicate that the questionnaire possesses unacceptable consistency. **Results.** A total of 57% of participants were informed about reproductive cell donation through the Internet, 29% by friends and family, and 11% of them were informed by doctors. Only 32% of participants were fully informed, and 25.1% were partially informed about the donation of reproductive material in the RS. Forty-three percent of participants were not informed about the donation of reproductive material. Most of the participants (54%) said they would maybe donate their reproductive material if they had more information, 20% would donate in any case, and 26% would refuse to donate reproductive material. **Conclusion.** The target group of potential donors of reproductive cells is present in the RS. In addition to the analysis of attitudes, further planning and implementation measures for the promotion of donation could have an influence on raising awareness about the lack of reproductive material and increase the recruitment of gamete donors.

Key words:
directed tissue donation; humans; reproduction; serbia; social marketing.

Apstrakt

Uvod/Cilj. Postoji konstantni porast potrebe za korišćenjem reproduktivnih ćelija trećih lica kod parova koji nemaju mogućnost začeća sa sopstvenim reproduktivnim ćelijama ili da bi se sprečilo prenošenje postojećeg naslednog genetskog poremećaja na dete. Cilj rada bio je da se teorijski prikaže i praktično analizira upotreba strategija socijalnog marketinga, korišćenjem prve tehnike analize stavova potencijalnih donora reproduktivnih ćelija u Republici Srbiji (RS), u interesu prilagođavanja ciljnoj grupi. **Metode**. Empirijsko istraživanje, u kome su učestvovale i žene i muškarci u RS, bilo je zasnovano na upitniku o spremnosti osoba da budu potencijalni donori reproduktivnih ćelija i o posedovanju informacija o donaciji reproduktivnih ćelija. U radu su podaci dobijeni tokom 2021. godine i upitnik je bio fokusiran na posebnu grupu stanovništva. Upitnik je poslat osobama životnog doba od 20 do 34 godine, koje bi mogle biti potencijalni davaoci reproduktivnih ćelija. U istraživanju je učestvovala 201 osoba ženskog i muškog pola, u RS. Prvi deo upitnika testiran je na internu konzistentnost, koja je testirana Kronbahovim proračunom alfa koeficijenta (α). Vrednosti α niže od 0,5 ukazuju na to da upitnik poseduje neprihvatljivu konzistentnost. **Rezultati.** Ukupno 57% ispitanika bilo je informisano o doniranju reproduktivnih ćelija putem

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interneta, 29% od strane prijatelja i porodice, a 11% je obavestio lekar. Samo 32% učesnika bilo je potpuno informisano, a 25,1% delimično informisano o donaciji reproduktivnog materijala u RS, dok 43% učesnika nije bilo obavešteno o donaciji reproduktivnog materijala. Većina učesnika, njih 54%, izjasnilo se da bi možda doniralo svoj reproduktivni material ukoliko bi imali više informacija, 20% bi doniralo u svakom slučaju, a 26% bi odbilo donaciju reproduktivnog materijala. **Zaključak**. Ciljna grupa potencijalnih davaoca reproduktivnih ćelija prisutna je u RS. Pored analize stavova, dalje planiranje implementacije mera za promociju doniranja moglo bi uticati na podizanje svesti o nedostatku reproduktivnog materijala i povećati odziv davaoca gameta.

Ključne reči:
tkivo, usmerena donacija; ljudi; reprodukcija; srbija; marketing, socijalni.

Introduction

Reproductive cell (gamete) donations are part of the infertility treatment with third-party assisted reproduction in which one of the partners is not a biological parent (sperm/oocyte donations) or both partners are not biological parents (embryo donation of newly created donated reproductive cells). The third party will not be involved in raising the child but agrees to donate their genetic material for reproductive purposes. Medical indications for using third-party reproductive cells are the inability to conceive with one's own reproductive cells, the lack of one's own reproductive cells, or an inherited genetic disease in order to prevent passing the disorder to the child. Therefore, reproductive cell donation is a health need that leads to the successful treatment of patients for whom it is the only form of infertility treatment. To recruit donors, it is necessary to educate the public about the concept of donations as well as about the possibility of donating reproductive material in the Republic of Serbia (RS). This would fill the reproductive cell bank. Information strategies include promotional campaigns that would shape the attitudes and decisions of potential donors.

In many European countries, there are not enough donors of reproductive cells; thus, recruitment is reduced, especially for egg donors. Even though media campaigns are launched to raise awareness in some countries, recruitment is reduced, and the shortage of reproductive cell donors is still present. Moreover, every year the number of recipients increases [mostly middle-aged (45–64 years) women], so there is a growing gap between supply and demand [1]. Data from the European Society for Human Reproduction and Embryology for 2011 show that there were 64,270 donations (egg donation and donor semen insemination) [2], while for 2016, that number almost doubled to 113,513 donations (egg donation and donor semen insemination) [3].

The procedure itself varies from one country to another due to legislative policies that regulate and guide organizational practice. A total of 30 countries offer treatments to single women, the use of donated sperm is allowed in 41 countries, and egg donation in 38 countries. The number of infants originating from the same sperm donor is different. This number ranges from one in Cyprus to 25 in the Netherlands. In seven out of 30 countries, the maximal number of families/women that may have children from the same sperm donor ranges from two in Slovenia to 12 in Denmark. The maximum number of infants originating from the same egg donor is defined in 25 countries, and the most common numbers are between four and six [4]. The first documented donor sperm insemination was performed in 1884 at Jefferson Medical College in the USA, while the first reported live birth from a donor egg occurred in Australia in 1983, quickly followed by another one in California in that same year [5].

Social marketing is a discipline that serves to influence the change of social behavior through research using social marketing methods and thus tries to solve social problems and participate in raising awareness about social dilemmas [6].

Social marketing uses marketing approaches like social marketing research and analysis for implementation and control of the implementation of social marketing strategies [6]. According to data from the updated publication of the Health Promotion Glossary of Terms 2021 published by the World Health Organization (WHO), the role of social marketing is to develop and integrate levels and concepts of marketing and thus influence behaviors that benefit individuals and communities. The practice of social marketing integrates research, practice, and theory and provides information on possible social change programs that are effective, efficient, equitable, and sustainable. It also includes creating a plan and implementing and controlling programs aimed at increasing the acceptability of social ideas and practices among target users. Social marketing methodologies are used for health communication and education in all countries [7].

A socially responsible approach is part of social marketing strategies. The first step in the implementation of social marketing strategies is the analysis of social problems through all aspects and with information that researchers could get and complete. The second step is to define social marketing strategies. The following steps are the implementation of marketing strategies and control of results in solving social problems. The goals of social marketing strategies are to raise awareness about social problems and define social marketing strategies in order to implement them. The final goal is to evaluate the results of solving social marketing problems, according to Wood [8].

Donor recruitment can be done on a reciprocal basis. A system built according to the rule of reciprocity where people who voluntarily accept they will benefit from the system should, therefore, contribute to that system as much as it is in accordance with their capacities. That is the so-called mirror gamete donation which can be achieved by setting up a system in which the partner of an infertile person donates gametes (as done in the Netherlands, Italy, France) [1].

The method of donor recruitment can be relational. In France, there is another principle of gamete donation – soli-

darity. Originally, there was the idea that a couple who has already got a child went to the French National Germ Cell Biobank (CECOS – *Centre d'étude et de conservation des oeufs et du sperme humains*) and thus tried to help another couple. This recruitment method is called the relational method because infertile couples sensitize friends or family in this way. This kind of donor recruitment enables faster treatment of couples who are before them on the waiting list in France [1].

One of the methods of recruiting donors is the so-called altruistic recruitment method. In Europe, the practice of donating body material is mainly oriented towards the altruistic model of donation. The condition of the altruistic model is that the donation is based on charitable motives, i.e., the desire to help others. However, this model fails to recruit a sufficient number of donors, which is why financial incentives (payments) have been proposed as a means of increasing the number of donors [9].

In some countries, there is a method of recruitment where basic expense costs are paid. Lack of consensus on whether the donor should receive money at all and, if so, what it should be for (for instance, payment for the service, compensation for lost earnings, or simply the minimum reimbursement of expenses incurred by the donor through the act of donation, e.g., travel expenses to the place of donation, etc.). The practice can be seen in the variety of laws and guidelines [10]. In Belgium, the costs ranged from 500 EUR to 2,000 EUR. Some centers offered nothing in exchange for egg donation, while others provided a complete free *in vitro* fertilization (IVF) cycle. In the Czech Republic, this amount is 560 EUR, in Finland 250 EUR, Greece from 900 EUR to 1,000 EUR, Poland from 935 EUR to 1,400 EUR, Portugal 650 EUR, Spain from 700 EUR to 1,300 EUR, Ukraine from 400 EUR to 640 EUR, and Great Britain fixed 870 EUR [11].

IVF programs are one type of donor recruitment practice. Women undergoing IVF may agree to donate excess eggs to infertile patients. This donor source is limited because this type of donation can be considered forced, especially if donors are offered a financial discount on their own IVF cycle [12]. In exchange for egg donation, some centers provide a completely free IVF cycle, which is the case in Belgium, while Poland funds the cycle partially, Ukraine also offers a partially funded IVF cycle, and, in the United Kingdom (UK), some offer a free full cycle, and some fund a part of the cycle [11].

Different motivations (incentives) of donors can lead to the decision of whether donors want to donate their reproductive material. One incentive could be to allow them to save their own reproductive cells (social freezing) specifically for egg donors; perhaps this could become a higher threshold of motivation to donate. Research shows that different donor motivations need to be evaluated because when it comes to egg donors, there is a risk, procedure, inconvenience, and time they spend for donation [13].

The first law on biomedically assisted fertilization (BMAF) in the RS is the Law on Treatment of Infertility and Procedures of Fertilization with Biomedical Assistance, first adopted in 2009 ("Official Gazette", No. 72/09). The law states that donations are allowed. However, the import and export of reproductive cells and surrogacy are prohibited. Pursuant to Article 42 of this Law, the Minister shall issue a license to one of the authorized health institutions referred to in paragraph 1 of this Article that will perform the activities of a bank of donated reproductive cells for the territory of the RS, by the law governing cell and tissue transplantation [14].

The second law, the Law on Biomedical Assisted Fertilization ("Official Gazette", No. 40/2017 and 113/2017-state law), was passed in 2017. The new law enables the import or export of reproductive cells if there is none in the "Bank"; it has also been extended to cases of preservation of fertility and social freezing, but surrogacy is prohibited. Although the first law on permitted donation was passed in 2009, there is still no documented data on the first gamete donation in the RS. Pursuant to Article 33 of the Law on BMAF, the prohibition of advertising referred to in paragraph 1 of this Article does not apply to the promotion of voluntary donation of reproductive cells and tissues, i.e., BMAF, which is organized and implemented by law [15].

The goal of the paper is to present a theoretical overview and perform a practical analysis of the use of social marketing strategies using the first technologies of analyzing the attitudes of potential donors of reproductive cells in the RS, which would go in the direction of more specific adaptation to the target group.

Methods

In this paper, a survey was conducted on a specific group of users who met one of the conditions (age) for a donation of reproductive cells and did a segmentation in order to assess the main desire of donors to get involved in the donation program and thus realize the offers and opportunities that are available today. Here, we analyze the supply through a communication strategy in the form of a questionnaire. Therefore, a Google questionnaire was designed with the main socio-demographic characteristics (age, marital status, education, reproductive history), reasons for donating (altruism, treatment, financial gain), information on donations, counseling, and choice of health institutions. The electronic survey was sent to 201 women and men aged between 20 and 34 years, including all social classes and geographical locations in the RS. We compared three groups of respondents using statistical analysis (those who would donate, those who would not, and those who might donate if they had more information about the donation). Nominal data were presented as frequencies with percentages and the corresponding 95% confidence intervals. Demographic characteristics and attitudes and opinions toward reproductive material donation are analyzed using a Chi-squared test and Fisher's exact test as appropriate. SPSS 21.0 (SPSS Inc., Chicago, Illinois) was used to perform statistical analyses. The level of statistical significance was set at $p < 0.05$. The questions from the first part of the questionnaires were tested for internal consistency, which was tested by Cronbach's alpha coefficient calculation (α). Values of α lower than 0.5 indicate that the questionnaire possesses unacceptable consistency.

Results

This study included 201 participants; 14 participants were excluded from the statistical analysis because they did not complete the questionnaire. The demographic characteristics of 187 participants are presented in Table 1. Most study participants were women; more than half were aged 30–34 years; two-thirds were highly educated, and almost 75% were employed. More than half of the participants were married or lived in extramarital unions. Forty percent of participants had children. The Cronbach's α value was 0.5, meaning the questionnaire is reliable. As the study did not have the aim to develop a questionnaire and, therefore, did not possess specific domains (constructs), this value confirms that the questionnaire may include these questions.

Attitudes and opinions toward reproductive material donation are presented in Tables 2 and 3. Forty-eight percent of participants met couples who needed help conceiving through *in vitro* fertilization, and 23% had personal experience with this issue. Less than half of the participants were fully informed, 38% partially, and 19% were not informed about the donation of reproductive material (eggs, sperm). Most (57%) of the participants were informed about reproductive cell donation through the Internet, 29% by friends and family, and 11% were informed by doctors. Only 32% of participants are fully informed, and 25.1% are partially informed about the donation of reproductive material in the RS. Forty-three percent of participants were not informed about the donation of reproductive material. Most (54%) of the participants said they would maybe donate their reproductive material if they had more information, 20% would donate in any case, and 26% would refuse reproductive material donation. Half (50.3%) of participants said that they would donate their material voluntarily, 22.5% would donate to a friend or relative, 16% to their partner, and 5.3% would donate with financial support. Only 21% of participants knew whom to contact in case of reproductive material donation. Sixty-nine percent of participants would choose a private clinic to perform the necessary analyses of their health condition, and 31% would choose a state clinic; 73.8% of participants said they would be more comfortable donating material in a private clinic; 70.6% would be motivated to donate reproductive material with compensation for free storage of their material for the future; 60.4% of participants knew that donations are anonymous. Almost all participants (93.6%) thought that the awareness of the people about donations of reproductive material should be raised through promotions – by conducting campaigns. In addition, 94.7% of participants thought that doctors could have an influence on raising people's awareness by encouraging patients and informing them about reproductive cell donations.

The questions from the first part of the questionnaire in Table 2 were tested for internal consistency. The Cronbach's α value was 0.5, which means that the questionnaire is reliable.

When attitudes and opinions toward the donation of reproductive material were compared between men and women, women more often reported they would choose a private clinic for necessary analyses of health conditions ($p = 0.019$) (Figure 1). Furthermore, women more often reported they would be more comfortable donating their reproductive material to a private institution ($p = 0.029$) (Figure 2).

Table 1

Demographic characteristics of participants

Parameter	Values	Bounds of 95% CI	
		lower	upper
Gender			
male	47 (25.1)	19.3	31.7
female	140 (74.9)	68.3	80.7
Age, years			
21–25	39 (20.9)	15.5	27.1
25–29	50 (26.7)	20.8	33.4
30–34	98 (52.4)	45.3	59.5
Education			
elementary	3 (1.6)	0.5	4.2
high school	59 (31.6)	25.2	38.5
college	125 (66.8)	59.9	73.3
Employment			
unemployed	27 (14.4)	10.0	20.0
student	21 (11.2)	7.3	16.3
employed	139 (74.3)	67.7	80.2
Marriage status			
married	70 (37.4)	30.7	44.5
single	72 (38.5)	31.7	45.6
extramarital union	45 (24.1)	18.4	30.6
Children			
yes	75 (40.1)	33.3	47.2
no	112 (59.9)	52.8	66.7

CI – confidence interval.
All values are expressed as numbers (percentages) or only percentages (for bounds of 95% CI).

Table 2

Attitudes and opinions toward reproductive material donation (the first part of the questionnaire)

Questions	Values	Bounds of 95% CI	
		lower	upper
Have you met couples who needed help conceiving through *in vitro* fertilization?			
yes, personal	43 (23)	17.4	29.4
no	54 (28.9)	22.7	35.7
friends/family	90 (48.1)	41.0	55.3
Are you informed about what it means to donate your reproductive material (eggs, sperm)?			
yes	79 (42.2)	35.3	49.4
partially	72 (38.5)	31.7	45.6
no	36 (19.3)	14.1	25.3
Do you know that you can donate your reproductive material (eggs and sperm) in the Republic of Serbia?			
yes	60 (32.1)	25.7	39.0
partially	47 (25.1)	19.3	31.7
no	80 (42.8)	35.8	49.9
Would you donate your reproductive material – eggs, sperm?			
yes	38 (20.3)	15.0	26.5
maybe, if I had more information	100 (53.5)	46.3	60.5
no	49 (26.2)	20.3	32.8
If you want to donate your reproductive material, do you know who to contact?			
yes	41 (21.9)	16.5	28.3
no	146 (78.1)	71.7	83.5
Would it motivate you to donate reproductive material with compensation for free storage of your material for the future – by freezing?			
yes	132 (70.6)	63.8	76.8
no	55 (29.4)	23.2	36.2
Do you know that donations are anonymous (without the possibility of knowing who the donors are and who received the reproductive material)?			
yes	113 (60.4)	53.3	67.2
no	74 (39.6)	32.8	46.7
Do you think that the awareness of the people about donations of reproductive material should be raised through promotions – by conducting campaigns?			
yes	175 (93.6)	89.4	96.4
no	12 (6.4)	3.6	10.6
Do you think that doctors can influence to raise people's awareness by encouraging patients by informing them about reproductive cell donations?			
yes	177 (94.7)	90.7	97.2
no	10 (5.3)	2.8	9.3

CI – confidence interval.
All values are expressed as numbers (percentages) or only percentages (for bounds of 95% CI).

Next, the demographic characteristics of participants were compared by donation decision in Table 4. There were no significant differences between donation status and gender and age. Education was significantly different between groups. In a group of participants who decided not to donate, most of them were highly educated people. In a group of participants who would donate reproductive material, half of them were married; the difference was significant according to donation status. There were no differences between donation opinion and children status.

Attitudes toward reproductive material donation according to donation opinion are shown in Table 5. According to the participant's donation opinions, knowing people who needed reproductive cell donation made no difference. Most of the participants who would donate their reproductive material were more informed about what it means; the difference was significant. Most of the participants who would refuse to donate reproductive material were informed through the Internet; the difference was close to the conventional level of significance ($p = 0.084$). Most of the participants who would donate reproductive material were informed through friends and family; the difference was close to the conventional level of significance ($p = 0.096$). Participants who would donate their reproductive material were more often informed about the donations in the RS; the difference was close to the conventional level of significance ($p = 0.092$).

Table 3

Attitudes and opinions toward reproductive material donation (the second part of the questionnaire)

Questions	Values	Bounds of 95% CI	
		lower	upper
Where did you hear the information about reproductive cell donations?			
not responded	6 (3.2)	1.4	6.5
internet	106 (56.7)	49.5	63.6
doctors	21 (11.2)	7.3	16.3
friends/family who needed help	54 (28.9)	22.7	35.7
What would be your motive if you wanted to donate reproductive material?			
not reported	11 (5.9)	3.2	9.9
altruism	94 (50.3)	43.1	57.4
financial	10 (5.3)	2.8	9.3
if my partner would need a donation	30 (16)	11.3	21.8
for a friend/relative	42 (22.5)	16.9	28.8
If you wanted to donate your reproductive material at some point, which institution would you choose to perform the necessary analyses of your health condition?			
state fertility clinic	58 (31)	24.7	37.9
private fertility clinic	129 (69)	62.1	75.3
Where would you be more comfortable donating your reproductive material, if you wish?			
state fertility clinic	49 (26.2)	20.3	32.8
private fertility clinic	138 (73.8)	67.2	79.7

CI – confidence interval.

All values are expressed as numbers (percentages) or only percentages (for bounds of 95% CI).

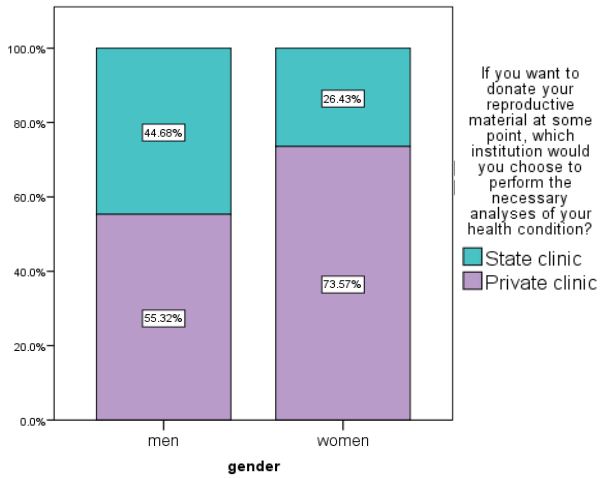

Fig. 1 – Institution selection between men and women for necessary analyses of health conditions.

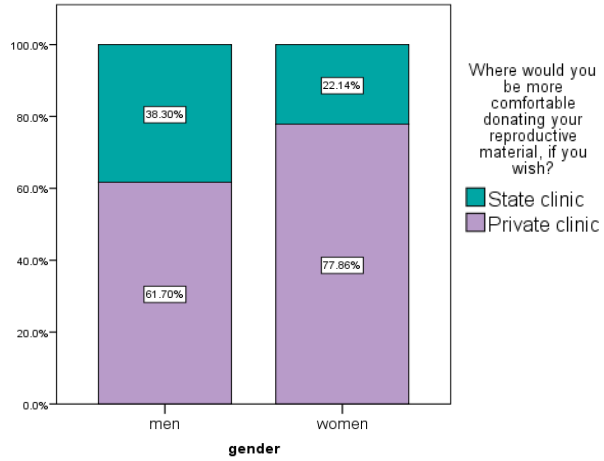

Fig. 2 – Institution selection between men and women for donation of reproductive material.

Table 4

Demographic characteristics of participants according to the decision about reproductive material donation

Parameter	Donation decision			
	yes	maybe	no	*p*
Gender				
male	13 (34.2)	24 (24)	10 (20.4)	0.314
female	25 (65.8)	76 (76)	39 (79.6)	
Age, years				
21–25	7 (18.4)	25 (25)	7 (14.3)	
25–29	7 (18.4)	24 (24)	19 (38.8)	0.135
30–34	24 (63.2)	51 (51)	23 (46.9)	
Education				
elementary	2 (5.3)	1 (1)	0 (0)	
high school	15 (39.5)	39 (39)	5 (10.2)	< 0.001
college	21 (55.3)	60 (60)	44 (89.8)	
Employment				
unemployed	7 (18.4)	11 (11)	9 (18.4)	
student	5 (13.2)	12 (12)	4 (8.2)	0.622
employed	26 (68.4)	77 (77)	36 (73.5)	
Marriage status				
married	19 (50)	36 (36)	15 (30.6)	
single	16 (42.1)	33 (33)	23 (46.9)	0.36
extramarital union	3 (7.9)	31 (31)	11 (22.4)	
Children				
yes	16 (42.1)	43 (43)	16 (32.7)	0.462
no	22 (57.9)	57 (57)	33 (67.3)	

All values are expressed as numbers (percentages).

Table 5

Attitudes and opinions toward reproductive material donation according to donation opinion

Parameter	Donation opinion			
	yes	maybe	no	*p*
Have you met couples who needed help conceiving through *in vitro* fertilization?				
yes, personal	11 (28.9)	21 (21)	11 (22.4)	
no	12 (31.6)	24 (24)	18 (36.7)	0.303
friends/family	15 (39.5)	55 (55)	20 (40.8)	
Are you informed about what it means to donate your reproductive material (eggs, sperm)?				
yes	25 (65.8)	35 (35)	19 (38.8)	
partially	6 (15.8)	49 (49)	17 (34.7)	0.002
no	7 (18.4)	16 (16)	13 (26.5)	
Where did you hear the information about reproductive cell donations?				
not responded	3 (7.9)	2 (2)	1 (2)	1.000
internet	15 (39.5)	59 (59)	32 (65.3)	0.084
doctors	6 (15.8)	8 (8)	7 (14.3)	0.273
friends/family who needed help	14 (36.8)	31 (31)	9 (18.4)	0.096
Do you know that you can donate your reproductive material (eggs and sperm) in the Republic of Serbia?				
yes	18 (47.4)	27 (27)	15 (30.6)	
partially	7 (18.4)	31 (31)	9 (18.4)	
no	13 (34.2)	42 (42)	25 (51)	0.092
What would be your motive if you wanted to donate reproductive material?				
not responded	0 (0)	1 (1)	10 (20.4)	< 0.001
altruism	26 (68.4)	56 (56)	12 (24.5)	0.003
financial	3 (7.9)	6 (6)	1 (2)	0.582
if my partner would need a donation	6 (15.8)	12 (12)	12 (24.5)	0.031
for a friend/relative	3 (7.9)	25 (25)	14 (28.6)	0.014
If you want to donate your reproductive material, do you know who to contact?				
yes	12 (31.6)	17 (17)	12 (24.5)	
no	26 (68.4)	83 (83)	37 (75.5)	0.159

Table 5 (continued)

Parameter	Donation opinion			
	yes	maybe	no	*p*
If you wanted to donate your reproductive material at some point, which institution would you choose to perform the necessary analyses of your health condition?				
state fertility clinic	15 (39.5)	31 (31)	12 (24.5)	
private fertility clinic	23 (60.5)	69 (69)	37 (75.5)	0.325
Where would you be more comfortable donating your reproductive material, if you wish?				
state fertility clinic	12 (31.6)	24 (24)	13 (26.5)	
private fertility clinic	26 (68.4)	76 (76)	36 (73.5)	0.663
Would it motivate you to donate reproductive material with compensation for free storage of your material for the future – by freezing?				
yes	32 (84.2)	79 (79)	21 (42.9)	
no	6 (15.8)	21 (21)	28 (57.1)	< 0.001
Do you know that donations are anonymous (without the possibility of knowing who the donors are and who received the reproductive material)?				
yes	27 (71.1)	56 (56)	30 (61.2)	
no	11 (28.9)	44 (44)	19 (38.8)	0.269
Do you think that the awareness of the people about donations of reproductive material should be raised through promotions – by conducting campaigns?				
yes	36 (94.7)	98 (98)	41 (83.7)	
no	2 (5.3)	2 (2)	8 (16.3)	0.003
Do you think that doctors can influence to raise people's awareness by encouraging patients by informing them about reproductive cell donations?				
yes	36 (94.7)	98 (98)	43 (87.8)	
no	2 (5.3)	2 (2)	6 (12.2)	0.033

Participants who would donate would more frequently voluntarily make a donation; the difference was significant compared to participants who would refuse to donate or those who would maybe donate reproductive material. Less than 10% of participants in all groups, according to donation status, would donate for financial compensation. There was no significant difference. Most of the participants who refuse to donate would change their opinion if their partner needed a donation; the difference was significant compared to participants who would donate or those who might donate reproductive material. Likewise, participants who would refuse to donate or who might donate would change their minds if a friend needed a donation. There was no significant difference between participants knowing whom to contact in case of reproductive material donation. Most participants in all three groups would choose private clinics to perform the necessary analyses; the difference was not significant according to donation opinion. Again, most participants reported that they would be more comfortable donating their materials in a private clinic; the difference was not significant according to donation opinion. Participants who would refuse to donate material would be significantly less motivated with compensation for free storage of their material for the future. Although most participants think that the awareness of the people about donations of reproductive material should be raised by promotions, those who would refuse to donate think this significantly less often. Likewise, those who would refuse to donate think significantly less often that doctors can have an influence in raising people's awareness by encouraging patients and informing them about reproductive cell donations.

Discussion

In order to meet the demand for reproductive material and the requirements of healthcare users whose medical indications require treatment of infertility with third-party assisted reproduction, the research tried to examine the possibility of potential supply and the opinion of the population of the RS on how to raise awareness of potential future reproductive cell donors and how to recruit donors to meet the patient's needs for donation services. Furthermore, the research tried to investigate the needs of donors as a target audience in order to perform a way of donating with as little stress as possible, the way they would like to be informed, the institutions they would prefer for their examination, and the reasons that would make them agree to donate their reproductive material, since a certain number of donors may be lost due to inadequate services. The application of marketing in healthcare has been criticized [16, 17] and made impossible for ethical reasons, and the question arises for further research as to which of the communication and promotional channels would be appropriate in order to provide the necessary information to reproductive material donors. Since the interpretation of ethics depends on the health policy and the quality of the legislative framework of the RS, this paper, by having an insight into public opinion, would present the necessary conditions that would satisfy potential donors and thus provide an understanding of the potential meeting of the supply.

Governments and clinics do not invest in public awareness campaigns or promote reproductive cell donations, so

donor recruitment is hampered by a lack of information, organization, and conditions. The United Kingdom has a National Gamete Donation Trust (NGDT), a body that raises awareness of the national shortage of sperm, egg, and embryo donors in the UK. This organization aims to recruit donors to reduce shortages and provides information on egg, sperm, and embryo donation and donor recruitment in the UK [9, 18]. In France, *Agence de la Biomedicine* has a similar role as the British NGDT [9].

In order to value the good that we get from donations, we should accept donors with mixed motives, as long as helping others is an important motive, as well as the characteristics of their motivation [9]. When it comes to egg donors, it can be argued that non-payment of donors is disrespectful and devalues the importance of their physical contribution and potential impact on their health [19].

Conclusion

Recruiting gamete donors is a complex issue. The target group of potential donors of reproductive cells exists in the RS. In addition to analyzing attitudes, further planning and implementation of certain attitudes could raise awareness about the lack of reproductive material and increase the recruitment of gamete donors. Experts and the government play a key role and need to address this issue. Reproductive cell donations, organization (procedure control), regulations, promotion, and population education should all be better regulated to raise public awareness of this problem. Currently, there is a shortage, little money is spent, and little effort is taken when it comes to awareness campaigns about germ cell donation. Constant effort in practical aspects would affect the recruitment of donors, and altruism and volunteering should not be absolute criteria as they currently are in the RS. An analysis of different conditions and rules of different systems of other countries can reveal a range of morally acceptable variants. We need creativity in designing a better system and flexibility in the application of existing systems of other countries if we want to cover the needs of donor gametes of patients of the RS so that they do not have to seek medical help outside their country if there is already a law whose small amendment could make great progress.

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Pseudotumor as adverse local tissue reaction due to implant corrosion

Pseudotumor kao lokalno neželjeno dejstvo usled korozije implanta

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Abstract

Introduction. The term adverse local tissue reactions (ALTRs) is used to describe pathologic tissue conditions appearing after total joint replacement, and it includes osteolysis, bone necrosis, muscle necrosis, cystic lesions, excessive fluid collections, soft tissue masses, pseudotumors, metal sensitivity, metallosis, and chronic inflammatory lesions. ALTRs are rarely described in the literature after the breakage of the ceramic components of the hip prosthesis. **Case report.** We present a case of a patient with massive fluid collections filled with metallic and tissue detritus, along with signs of systemic cobalt (Co) and chromium (Cr) intoxication. Symptoms developed after revision of the acetabular component with the application of a metal-on-polyethylene coupling. Previously, several revisions were made due to breakage of the ceramic components of the endoprosthesis and instability of the hip. After removal of pseudotumor masses and revision of all components of the endoprosthesis with implantation of a coupling between the ceramic head and the polyethylene insert, there was a significant drop in the serum values of Co and Cr. **Conclusion.** Trunnion damage should be assessed during revision procedures, and if present, both prosthetic components should be replaced to prevent disastrous effects of metallic corrosion, ALTRs, and systemic metallic ions intoxication. Measurement of serum levels of Co and Cr in patients after joint replacement could identify patients at risk for the development of ALTRs and metallosis.

Key words:
arthroplasty, replacement, hip; chromium; cobalt; long term adverse effects; prostheses and implants; tissues.

Apstrakt

Uvod. Termin neželjene lokalne reakcije tkiva (NLRT) odnosi se na patološke promene tkiva koje se javljaju nakon totalne zamene zgloba i uključuje osteolizu, nekrozu kosti, nekrozu mišića, cistične promene, prekomerno nakupljanje tečnosti oko zglobova, pojavu mekotkivnih pseudotumora, reakciju preosetljivosti na metal, metaloze tkiva i hronične inflamacijske lezije. U literaturi su retko opisivane NLRT nastale nakon pucanja keramičkih komponenti endoproteze kuka. **Prikaz bolesnika.** Prikazujemo slučaj bolesnika sa masivnim tečnim kolekcijama ispunjenim metalnim i tkivnim detritusom i znacima sistemske intoksikacije jonima kobalta (*cobalt* – Co) i hroma (*chromium* – Cr). Simptomi su se razvili nakon revizije acetabularne komponente uz primenu metal-na polietilen oslanjajućeg para. Prethodno je učinjeno više revizija zbog pucanja keramičkih komponenti endoproteze i nestabilnosti kuka. Nakon uklanjanja pseudotumorskih masa i revizije svih komponenti endoproteze sa implantacijom oslanjajućeg para između keramičke glave i polietilenskog inserta, došlo je do značajnog pada nivoa Co i Cr u serumu. **Zaključak.** Tokom revizionih procedura treba proceniti oštećenje truniona (*trunnion*) i ukoliko ono postoji, potrebno je zameniti obe protetske komponente, kako bi se sprečili efekti korozije metala, NLRT i sistemska intoksikacija jonima metala. Merenjem nivoa Co i Cr u serumu kod bolesnika posle totalne artroplastike, mogu se prepoznati oni bolesnici koji imaju rizik od nastanka NLRT.

Ključne reči:
artroplastika kuka; hrom; kobalt; neželjeni efekti, dugoročni; proteze i implantati; tkiva.

Introduction

The term adverse local tissue reactions (ALTRs) has been used more often to describe pathologic tissue conditions appearing after total joint replacement, and it includes osteolysis, bone necrosis, muscle necrosis, cystic lesions, excessive fluid collections, soft tissue masses, pseudotumors, metal sensitivity in the form of aseptic

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lymphocyte-dominated vasculitis-associated lesions, metallosis, and chronic inflammatory lesions [1]. Recently, ALTRs have been noticed around metal-on-metal (MoM) articulations more often [2]. Damage to the femoral stem neck and head–neck junction (trunnion) of cobalt (Co) and chromium (Cr) components of the implants leads to an increase in the serum levels of metallic ions and local tissue reactions [3].

We present a patient in whom breakage of the ceramic components led to damage of the stem neck and consequent local tissue reaction which deteriorated after partial revision of the bearing surfaces. The patient developed a systemic manifestation of Co and Cr poisoning.

Case report

A 57-year-old man has been admitted to the hospital because of pain and pelvic mass. Initially, total hip replacement was performed at the age of 50 due to avascular necrosis of the hip and consequent degenerative hip disease. Initial total hip replacement was performed in 2005 with ceramic-on-ceramic (CoC) coupling (Zimmer Trilogy AB acetabular component, Fiber Metal Midcoat stem, Biolox forte alumina, ceramic head 28 mm) (Figure 1).

Fig. 1 – Postoperative X-ray showing unremarkable implant position.

In 2007, two years after index surgery, atraumatic breakage of the ceramic acetabular insert occurred. The revision was performed by replacing the ceramic components solely (Zimmer Trilogy AB acetabular component, Fiber Metal Midcoat stem, Biolox forte alumina, ceramic head 28 mm) (Figure 2). No significant debris was encountered at that time.

Fig. 2 – X-ray after first revision surgery showing replaced ceramic insert and modular head with retained initial acetabular and femoral components.

In 2010, three years after the first revision surgery, another breakage occurred, this time of both ceramic components (Figure 3).

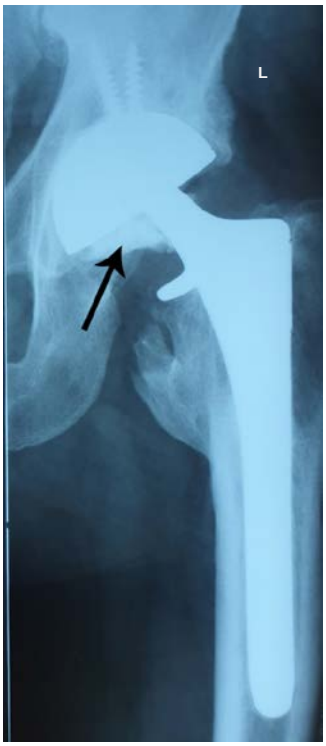

Fig. 3 – X-ray depicts breakage of prosthetic ceramic head and insert (arrow).

Another revision was done by the same surgeon using the previous incision through a posterolateral approach. The acetabular component was revised with a constrained liner, with metal-on-polyethylene (MoP) coupling with titanium aluminum vanadium (TiAlV) alloy consisting of CoCr head and polyethylene liner with stainless steel ring [Zimmer Trilogy acetabular component, ultra-high molecular weight polyethylene (UHMWPE), CoCr ceramic head 28 mm]. No damage to the femoral stem and neck was notified and mentioned in the report (Figure 4).

Fig. 4 – X-ray after revision hip arthroplasty with acetabular replacement and constrained polyethylene liner insertion.

In 2011, the patient started to complain about pain and discomfort in the inguinal and gluteal region with ataxic episodes and hearing and seeing impairment, and a constant feeling of fatigue. The symptoms were evolving rapidly and the patient was admitted to our hospital for a large pelvic and abdominal mass. These symptoms were accompanied by elevated blood Co and Cr levels – 133.9 μg/L and 40.3 μg/L, respectively. Multidetector computed tomography (MDCT) showed large intra-abdominal masses and collections (Figure 5).

In December 2012, he was prepared for surgery, and multiple lobulated tissue formations filled with dark fluid were removed from the inferior pelvic wall and retroabdominal musculature, which was infiltrated by metallic debris and dark greyish fluid (Figure 6).

A subsequent pathohistological examination confirmed metallosis. The laboratory markers of inflammation were slightly elevated – C-reactive protein 7.7 mg/L [reference value (RR) up to 5 mg/L], erythrocyte sedimentation rate 2 mm/h (RR up to 10 mm/h), fibrinogen 3.5 g/L (RR 2–4 g/L). Metallic head and stem neck trunnion were reduced in size, and polyethylene showed signs of gross wear (Figure 7).

Fig. 5 – Large pseudotumor mass (279 × 94 × 59.3 mm) depicted on multidetector computer tomography (arrows).

Fig. 6 – Part of the excised intrapelvic mass.

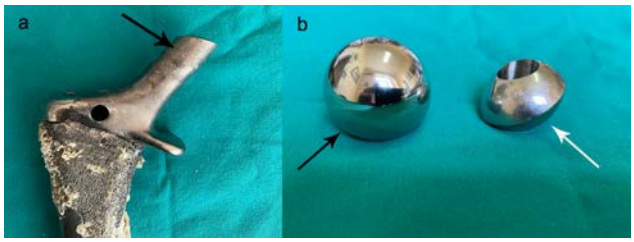

Fig. 7 – a) Extracted femoral stem showing the altered shape of the head–neck junction (arrow); b) Extracted modular metal head (28 mm diameter) with severe damage and size reduction (white arrow); regular modular metal head (32 mm diameter) for comparison (black arrow).

Prosthetic components were removed, and the joint was thoroughly debrided. There were no signs of infection, and tissue cultures remained sterile.

In July 2013, seven months after the removal of pseudotumor masses and explantation of endoprosthesis, another revision was performed, and a modular revision stem was implanted with a ceramic head and polyethylene liner coupling (Zimmer Modular Revision stem, Zimmer Trilogy acetabular component, and UHMWPE liner, ceramic head 32 mm) which consists of a stem and shell made of Ti/Va/Al alloy with a polyethylene acetabular insert and ceramic modular head (Figure 8).

Fig. 8 – X-ray image after final revision with residual metal particles in the periarticular tissue resembling heterotopic ossification.

The patient recovered to unassisted walking. His hearing and sight loss did not recover. At the last follow–up in 2021, his hip was pain-free and functional, and serum Co and Cr levels were within normal values (1.5 μg/L and 4.2 μg/L, respectively).

Discussion

The patient described in this case report had a large ALTR in the lower abdominal region and around the involved hip in the form of metallosis and the development of a pseudotumorous mass. Initial damage of the stem neck after ceramic components breakage was not recognized during the first and second revisions. Revision to a metallic modular head-on acetabular poly-constrained component led to progressive severe destruction of stem neck and head junction and an increase of metallic debris. The consequent formation of semi-liquid masses around the hip had progressed to the pelvic cavity and lower abdomen.

Ceramic articulations are less tolerant to malposition of the components, which most often results in increased posterior edge loading when acetabular cups are positioned in excessive abduction. The fact that several hip dislocations were reported in the presented case in the interval between revisions for implant fracture points to the existence of this problem. Fracture of the ceramic component produces particles that act as a third body after revision and can produce wear to the revised components [3].

The most attributable cause of this condition is fretting corrosion in the head–neck junction and acetabular ring impinging on the stem neck, which was probably already damaged by fractured ceramic particles from previous surgeries. Metallic particles had led to irritation and fluid accumulation in the bursa and granuloma formation around foreign body material. The severity of the damage to the head and neck components and the appearance of the retrieved components could suggest that fretting could not be the sole cause of the damage. Differences in electrical potential may cause galvanic corrosion when two different metals are in contact in an electrolyte solution [4].

Trunnion corrosion is identified as a possible cause of fulminant pseudotumors [5]. The increase in MoM implant usage in the early 2000s led to the recognition of more frequent metal-associated ALTRs and the need for early revision [6]. Further research on this problem has led to new diagnostic tools such as metal ion level tests and metal hypersensitivity tests [7, 8]. Subsequently, metal-associated tissue destruction was also found in implants with MoP-bearing material [9].

ALTRs are registered in about 10% of patients with MoM hip implants and a lower but unknown number of patients with mostly used MoP hip implants [10].

The Co and Cr ions levels in serum could be elevated after hip replacement, although routine serum level determinations are usually not performed. The cut-off for metal ion levels for risks of clinical complications is 7 μg/L [11]. The increase of Co and Cr ions in serum could lead to systemic body manifestations, which could be very variable, ranging from skin rash and nausea to progressive cardiac insufficiency, renal failure, hearing impairment, and loss of vision [12].

Measuring serum levels of metal ions has a diagnostic value not only for systemic exposure to metallic ions but also for the wear of the metallic parts of implants, which indicates the possibility of adverse reactions around the affected implant. Elevated ion levels could suggest trunnion damage and wear as a source of metallosis and likely cause of pseudotumor formation.

In most cases, pseudotumor formations after CoC implant couplings could be attributed to stem neck damage and corrosion or metallic debris from the stem coating [3, 13]. Measuring serum levels of Co and Cr is useful in such situations and could indicate mechanical damage to the components that are difficult to confirm by other diagnostic tools.

Due to a usual absence of pain in the affected hip, differential diagnosis of the ALTRs could be difficult and should consider soft tissue problems such as psoas tendonitis and bursitis, referred pain from spinal disorders, and inguinal or abdominal hernias. Multidetector computer tomography scan could be helpful in the evaluation of the component position; magnetic resonance imaging could be helpful in the evaluation of pelvic and abdominal masses and fluid collections. Bone scintigraphy can indicate infection or loosening.

Conclusion

Trunnion damage assessment during revision procedures should be mandatory. The surgeons are urged to consider trunnion lesions during revisions, especially after the breakage of ceramic components. If trunnion damage exists, it is necessary to replace both prosthetic components, even if they are well fixed, in order to prevent disastrous effects of metallic corrosion, ALTRs, and systemic intoxication by the metallic ions.

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CASE REPORT
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Giant left main coronary artery aneurysm

Ogromna aneurizma leve glavne koronarne arterije

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Abstract

Introduction. Coronary artery aneurysms (CAAs) are rare disorders, especially the left main CAA. In the literature, there are several reported cases with CAAs, various localization, size, clinical presentation, and way of treatment. There is no unique consensus about the most adequate treatment for these patients; however, surgery is still preferable, although there are some new experiences of percutaneous treatment. The decision is made for each patient individually. We report a case of giant left main CAA, with acute coronary syndrome and heart failure presentation, surgically treated. **Case report.** A 66-year-old female patient was admitted to the emergency department of our clinic due to chest pain and dyspnea. Acute non-ST-elevation segment myocardial infarction (STEMI) of anterolateral localization was diagnosed (creatine kinase max 1,111 U/L, troponin T 3.754 ng/mL), complicated with acute heart failure. Heart catheterization and coronary angiography revealed a giant saccular, 3.5 × 3.5 mm left main CAA full with thrombi, compressing the proximal segments of the left anterior descending and circumflex artery. **Conclusion**. Giant left main CAAs are rare pathologic findings, and there are no established principles for treatment. Although the percutaneous way of treatment is now available in selected cases, the surgical approach is still preferred for these patients.

Key words:
cardiac catheterization; coronary aneurysm; coronary angiography; cardiac surgical procedures; diagnosis; non-st elevated myocardial infarction.

Apstrakt

Uvod. Aneurizme koronarnih arterija (KA) su retki poremećaji, naročito aneurizme glavnog stabla leve KA. U literaturi je opisano više slučajeva aneurizmi KA, različite lokalizacije, veličine, kliničke slike i načina lečenja. Ne postoji jedinstven stav o najadekvatnijem načinu lečenja kod tih bolesnika. Međutim, i dalje je poželjniji operativni način lečenja, mada je moguć i perkutani način lečenja. Odluka se donosi za svakog bolesnika pojedinačno. Prikazan je redak slučaj bolesnika, lečenog hirurškim putem, sa velikom aneurizmom glavnog stabla leve KA, koja se prezentovala akutnim koronarnim sindromom i srčanom insuficijencijom. **Prikaz bolesnika.** Bolesnica stara 66 godina primljena je u urgentni centar naše klinike zbog bolova u grudima i dispneje. Dijagnostikovan je akutni infarkt miokarda bez elevacije ST segmenta anterolateralne lokalizacije (maksimalne vrednosti kreatin kinaze 1 111 U/L, troponina T 3,754 ng/mL), komplikovan akutnom srčanom insuficijencijom. Kateterizacijom srca i koronarografijom otkrivena je ogromna (3,5 × 3,5 mm) sakularna aneurizma glavnog stable leve KA, puna tromba, koja je pritiskala proksimalne segmente leve prednje silazne i cirkumfleksne arterije. **Zaključak.** Ogromne aneurizme leve glavne KA su redak patološki nalaz i ne postoje utvrđeni principi lečenja. Mada je perkutani način lečenja sada dostupan u odabranim slučajevima, za te bolesnike je i dalje poželjan hirurški pristup.

Ključne reči:
kateterizacija srca; aneurizma, koronarna; hirurgija, kardijalna, procedure; dijagnoza; angiografija koronarnih arterija; infarkt miokarda bez st-elevacije.

Introduction

There are two entities of coronary arteries enlargement – coronary artery ectasias (CAEs) and coronary artery aneurysms (CAAs). CAEs refer to diffuse dilatation up to 50% of the largest diameter, and CAAs are defined as localized dilatation which exceeds the largest vessel diameter by > 50%. CAAs are very rare, and the overall incidence is 0.3–5.3% [1].

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Left main CAAs are extremely rare, with an incidence of 0.1% found by Topaz et al. among 22,000 coronary angiograms [2]. The lowest incidence of 0.02% is shown for giant CAAs, while the highest incidence of 5.9% is reported for those associated with congenital artery fistula [3]. "Giant aneurysms" are those whose diameter exceeds 2 cm [1–3]. Owing to their rarity, there are no unique guidelines for their treatment. Therefore, case reports are important for discussing individual strategies. We present a patient with symptomatic giant left main CAA presented as acute myocardial infarction and severe left ventricle dysfunction.

Case report

A 66-year-old female patient was admitted to the emergency department of our clinic due to chest pain and dyspnea. Acute non-ST-elevation segment myocardial infarction (non-STEMI) of anterolateral localization was diagnosed [creatine kinase max 1,111 U/L, normal range (NR): 0–200 U/L; troponin T 3.754 ng/mL, NR: < 0.3 ng/mL], complicated with acute heart failure. She had never been treated for cardiovascular disorders before. According to her past medical history, she has been suffering from hypertension and hypothyreosis for a long time; both were under medication control. Physical examination revealed the following: inspiratory crackles; normal loudness of heart sounds with gallop rhythm of 120 bpm; a systolic regurgitation heart murmur was heard at the apex and parasternal area; blood pressure was 110/80 mmHg. She was monitored closely.

Assessment

Electrocardiography findings showed sinus tachycardia with ST depression in several leads: DI and aVL, V2–V6, and slight ST-elevation in aVR. On chest X-ray, an enlarged heart silhouette and pulmonary congestion were revealed. Echocardiography revealed signs of ischemic cardiomyopathy with hypo- to akinetic septum, lateral and anterior wall, reduced ejection fraction (EF) 25–30% (NR ≤ 50%), and significant secondary mitral regurgitation (3–4+). Heart catheterization and coronary angiography revealed a giant saccular, 3.5 × 3.5 mm left main CAA full with thrombi, compressing the proximal segments of the left anterior descending (LAD) and circumflex (Cx) artery (Figure 1). Prior to decision of the further treatment, a high-resolute computed tomography imaging study was performed. The giant saccular thrombotic left main CAA also completely compressed the origin of the LAD and Cx coronaries (Figures 2 and 3). We also performed immunology analyses to exclude vasculitis.

Fig. 1 – Coronary angiography shows a large left main coronary artery aneurysm (arrow), full with thrombus, compressing left anterior descending and circumflex coronary artery.

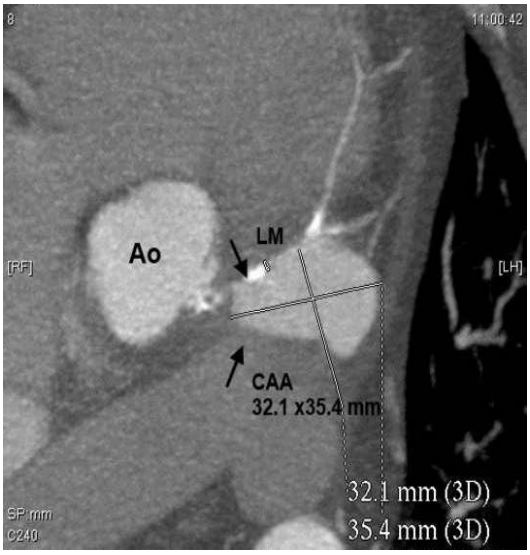


Fig. 2 – Multislice computed tomography imaging study confirmation of left main (LM) coronary artery aneurysm (CAA) (lower arrow). Ao – aorta.

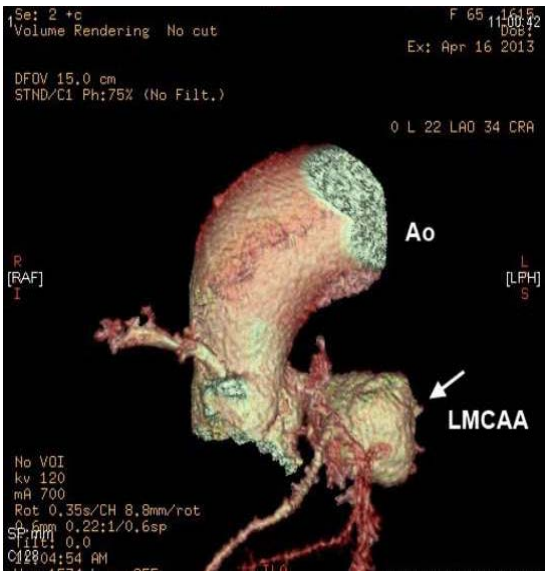


Fig. 3 – Volume rendered computed tomography imaging study of left main coronary artery aneurysm (LMCAA) (arrow). Ao – aorta.

Intervention

The patient was treated with anticoagulation therapy, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, mineralocorticoid receptor antagonists antagonists, loop diuretics, and statins. When the stable condition was achieved with complete resolution of acute myocardial injury, cardiac surgery was performed with resection (Figure 4 A and B) and aneurysmorrhaphy and two by-passes: left internal mammary artery (LIMA) on LAD and saphenous vein graft – on first obtuse marginal (OM) branch. The histopathology of the CAA wall suggested that the etiology was an atherosclerotic change.

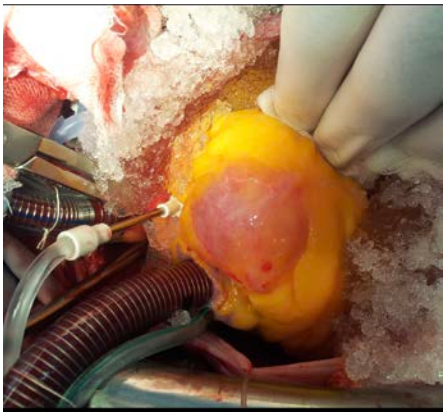
Outcomes

Control computed tomography imaging study was performed one month after the operation (Figure 5). It showed patency of LIMA graft and advanced atherosclerotic lesions on saphenous vein graft on the first OM branch, without significant stenosis. Clinically, the patient was relieved of symptoms despite the persistence of poor EF (ischemic dilated cardiomyopathy and heart insufficiency).

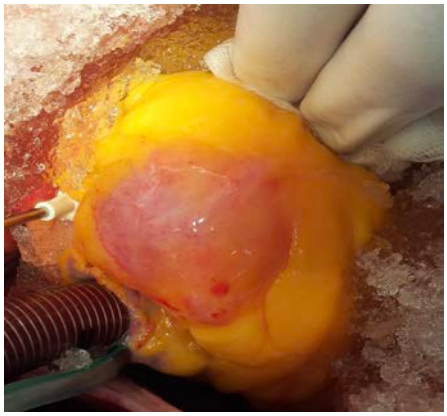
Discussion

CAAs are rare anomalies with various incidences regarding localization. The most common anomalies are the right CAAs (rCAAs) (40%), followed by the LAD artery (32%), the left Cx artery aneurysms (17%), and the left main CAAs (3.5%) as the rarest localization [4, 5]. CAAs can be divided into true and false (pseudoaneurism) depending on vessel wall composition. They can also be stratified as fusiform (longitudinal diameter is larger than transverse diameter) or saccular (transverse diameter is larger than longitudinal diameter) [5, 6].

The majority of them have atherosclerotic origin and account for > 90% of CAAs in adults [2]. Other causes are inflammatory vascular disorders (systemic lupus erythematosus, polyarteritis nodosa, Kawasaki disease, etc.) and connective tissue disorders (Ehlers-Danlos syndrome, Marfan's syndrome, scleroderma). Some infectious diseases, such as infective endocarditis, can also cause CAAs, as described in a few case studies [7]. Congenital etiology of aneurysms is usually accompanied by coronary artery fistulas [8]. In our case, we excluded systemic vascular etiology performed by immunology analysis, and pathohistology confirmed atherosclerotic origin.



A



B

Fig. 4 – Giant left main coronary artery aneurysm during surgery (A) and evacuation (B).

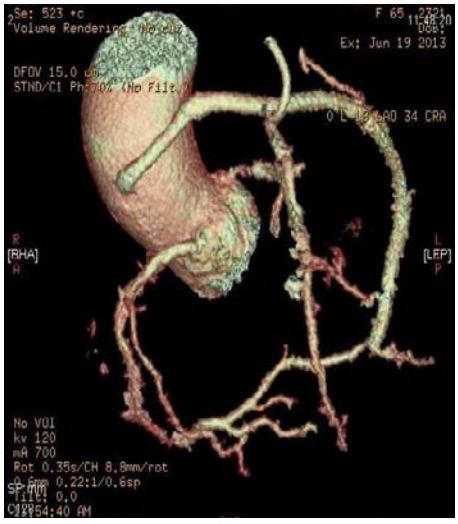


Fig. 5 – Volume rendered computed tomography imaging study after one month of surgical treatment.

Increasing the use of percutaneous interventional treatment in cardiology is also one of the common causes of CAA. Injury of the media of blood vessels due to the extension of the atherosclerotic process and the percutaneous procedure is the probable pathologic mechanism. It has been noticed that balloon dilatation with inadequate balloon size leads to CAA over time. Furthermore, patients with dissection after percutaneous coronary intervention (PCI) have a higher chance of developing CAA. It was also described that first-generation drug-eluting stents could precipitate coronary aneurysms. Over time after implantation, embedded drug stent (sirolimus or paclitaxel) can consequently cause hypersensitive and inflammatory reactions with wall weakness and dilatation [1, 2].

Clinical presentations can be various. Small CAAs are usually asymptomatic. Sometimes they disguise as an anterior mediastinal mass [9]. Myocardial ischemia could be developed due to spasms of the affected artery or distal embolization from thrombotic lesions in the CAA. If these are frequent, large infarction could develop, followed by signs and symptoms of heart failure, as described in our case. CAAs are also prone to progressive enlargement, possible rupture, and potential development of hematopericadium or cardiac tamponade [2].

Diagnostic tools could be invasive and noninvasive. Echocardiography is a noninvasive method for diagnosis of the left main coronary aneurysm, but it can visualize just the proximal segments of coronary arteries [4, 5]. Multidetector computed tomography of coronary arteries is one of the imaging methods for diagnosis, but the "gold standard" is invasive coronary angiography, especially along with the concomitant intravascular ultrasound use. They give us information about the size, shape, location, presence, and number of coexisting anomalies, as well as information about CAA wall structure. It can also suggest atherosclerosis as the underlying condition [4].

Currently, the optimal management strategy of CAAs remains challenging due to the lack of published outcome data. The evidence suggests that asymptomatic small CAAs may not require any treatment, just optimal medication therapy and regular follow-up. The final decision should be individualized depending on size, location, and clinical context. In symptomatic patients marked as unsuitable for PCI, surgical excision is the preferred option [10].

All patients should receive an aggressive modification of coronary risk factors whether or not obstructive coronary artery disease is present [10]. Medicament treatment alone encompasses observation, anticoagulation therapy, and antiplatelet therapy in case of atherosclerotic etiology. Yan et al. [11] suggest that novel oral anticoagulants may be suitable for CAA treatment. Some authors emphasize the important role of elevated levels of matrix metalloproteinase-3 in CAA's development; therefore, statin therapy is of crucial importance [12]. Avoiding nitrates in these patients due to possible steal syndrome and exacerbation of angina is also advocated. Gulec et al. [13] found that the polymorphism of the ACE gene is a potent risk factor for CAA. Thus, the use of ACE inhibitors in CAA's therapy to prevent dilatation progression is advocated; however, it has not been proven yet. Accordingly, our patient received a proper medication treatment with significant symptom improvement. Nevertheless, pharmacotherapy is the only prevention of possible complications of CAA, but definite treatment should be either percutaneous stent implantation or surgical treatment. Still, limited evidence is available on the effectiveness and safety of this interventional practice. Yet, there is limited evidence available on the effectiveness and safety of percutaneous interventional practice.

Treatment of CAAs with covered stents has been reported in several case reports; however, there is limited evidence available on the effectiveness and safety of this interventional practice [14]. Burzotta et al. [15] suggested the use of the self-expandable Symbiot PTFE-covered stent for percutaneous treatment of a large coronary aneurysm.

Win et al. [16] described a case of a large fusiform aneurysm, successfully treated with a technique of stent-assisted coil embolization. Dai et al. [17] suggest that multiple overlapping stents might be a promising therapeutic target for CAAs. Some authors also described interventional complications as prolapse of the covered stent into CAA due to significant LAD motion during the cardiac cycle [18]. However, surgery is the preferred way of treatment in patients with giant, symptomatic CAAs [19, 20].

Indications for surgery treatment are the following: severe coronary artery disease, CAAs near the bifurcation of large branches, evidence of emboli from the aneurysm to the distal coronary bed resulting in myocardial ischemia, progressive enlargement of a CAA documented by serial angiographic measurements during follow up, CAAs in the left main stem, complications such as fistula formation or compression of cardiac chambers, and giant CAAs [2]. In our case, surgical treatment was undertaken due to the giant size and specific localization of CAA with compression of proximal segments of LAD and Cx arteries and evidence of embolization as well.

There are various surgical strategies, such as resection, reconstruction, and exclusion with a bypass operation. Since there is no typical surgical approach for giant coronary aneurysms, the decision has still been made on an individual basis [20]. The prognosis of CAA depends on the size of the aneurysm. Small aneurysms have a favorable prognosis with a low risk of myocardial ischemic events and/or mortality and giant CAAs have a worse prognosis due to common complications. Baman et al. [21] predicted a 5-year mortality rate of 29.1% among patients with CAAs. They found no statistically significant difference between the survival curves of aneurysmal patients with and without obstructive coronary artery disease.

Conclusion

Giant left main CAAs are rare pathologic findings and there are no established principles for treatment. Although the percutaneous way of treatment is now available in selected cases, the surgical approach is still preferred for these patients.

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CASE REPORT

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From simple neck pain to the diagnosis of Langerhans cell histiocytosis in the thyroid gland

Od bola u vratu do dijagnoze histiocitoze Langerhansovih ćelija u štitastoj žlezdi

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Abstract

Introduction. Langerhans cell histiocytosis (LCH), as a hematopoietic neoplasm, is a clonal proliferation of Langerhans dendritic cells. A comprehensive clinical examination is sometimes crucial for detecting rare adult diseases, such as LCH with concomitant autoimmune thyroid disease. **Case report.** A 43-year-old female patient first presented for an endocrinology consultation due to front neck pain and swelling accompanied by fatigue and malaise. The physical examination revealed an enlarged right thyroid gland lobe of extremely firm consistency that was painfully tender on palpation. Echosonographic findings confirmed that the right thyroid gland lobe was enlarged and was not clearly demarcated from the surrounding tissue while exhibiting pronounced parenchyma inhomogeneity characterized by reduced echogenicity of the anterior aspect and pronounced hypoechoicity of the posterior aspect, permeated with fibrous bands and calcifications. The structure of the left thyroid lobe was pseudonodular, with the characteristics of a chronic inflammatory process. Biohumoral findings indicated chronic autoimmune thyroiditis and primary hypothyroidism. Medical history, clinical findings, and personal and family predisposition to malignancy confirmed the need for accelerated additional diagnosis. Fine-needle aspiration biopsy was indicative of atypia of undetermined significance involving Hurthle cells, nuclear overlaps, anisocytosis, anisonucleosis, and the presence of nuclear incisions. Analyses performed after thyroidectomy pointed to the fibrous form of chronic thyroiditis, with suspected monoclonal proliferation of histiocytic and/or lymphoid cells. Immunohistochemical findings confirmed Hashimoto's thyroiditis and LCH. As the postoperative course was favorable, the patient was prescribed L-thyroxine replacement therapy, along with continuous and systematic monitoring for histiocytosis. **Conclusion.** Histiocytosis should be suspected more often, given the high incidence of autoimmune thyroid disease in adulthood. A timely LCH diagnosis largely determines the outcome.

Key words:
diagnosis, differential; histiocytosis, langerhans-cell; histological techniques; immunohistochemistry.

Apstrakt

Uvod. Histiocitoza Langerhansovih ćelija (HLĆ), hematopoetska neoplazma, predstavlja klonsku proliferaciju Langerhansovih dendritskih ćelija. Detaljan klinički pregled ponekad je presudan za otkrivanje retkih bolesti odraslog doba, kao što je HLĆ sa prisutnom autoimunskom bolešću štitaste žlezde. **Prikaz bolesnika.** Žena stara 43 godine prvi put se javila na pregled kod endokrinologa zbog bolova i otoka prednjeg dela vrata, praćenog umorom i malaksalošću. Inspekcijom i palpacijom utvrđen je uvećan desni režanj štitaste žlezde, izuzetno čvrste konzistencije, bolno osetljiv pri palpaciji. Ehosonografskim pregledom zapažen je uvećan desni režanj štitaste žlezde, nejasno ograničen od okolnog tkiva, sa izrazito nehomogenim parenhimom, smanjenom ehogenošću anteriornog aspekta i izraženom hipoehogenošću posteriornog aspekta parenhima štitaste žlezde, prožet fibroznim trakama i kalcifikacijama. Viđena je pseudonodularno izmenjena struktura levog režnja štitaste žlezde, sa karakteristikama hroničnog zapaljenskog procesa. Biohumoralni nalaz je ukazivao na hronični autoimunski tiroiditis i primarnu hipotireozu. Anamneza, klinički nalaz, lična i porodična sklonost ka malignitetu zahtevali su ubrzanu dopunsku dijagnostiku. Rezultat aspiracione biopsije tankom iglom odgovarao je atipiji neodređene značajnosti sa Hurthleovim ćelijama, nuklearnim preklapanjima, anizocitozom, anizonukleozom i prisustvom nuklearnih useka.

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Patohistološki nalaz nakon tireoidektomije odgovarao je fibroznoj formi hroničnog tiroiditisa, sa sumnjom na postojanje monoklonalne proliferacije histiocitnih i/ili limfoidnih ćelija. Imunohistohemijski nalaz potvrdio je Hashimoto tiroiditis i HLĆ. Postoperativni tok prošao je bez komplikacija i bolesnici je uvedena supstituciona terapija L-tiroksinom, uz nastavak kontinuiranog i sistemskog praćenja u pogledu histiocitoze. **Zaključak.** Na HLĆ treba češće posumnjati s obzirom na visoku učestalost autoimunske bolesti štitaste žlezde u odraslom životnom dobu. Pravovremena dijagnoza HLĆ u velikoj meri određuje ishod lečenja.

Ključne reči:
dijagnoza, diferencijalna; langerhansove ćelije, histiocitoza; histološke tehnike; imunohistohemija.

Introduction

Langerhans cell (LC) histiocytosis (LCH), as a hematopoietic neoplasm, is a rare granulomatous disease characterized by the proliferation of mononuclear dendritic cells (DC) in certain tissues and organs with an incidence of 4.0−5.4 per million individuals [1].

LCH can be unifocal or multifocal, whereby classification is based on the involvement of specific organs or organ systems. The diagnosis is confirmed by electron microscopy or immunohistochemical (IH) reactivity of histiocytes to CD1a and/or S-100 proteins [2]. The International Association for Histiocytosis has developed a risk prognostic system according to the prevalence, functional disorder severity, and age. According to these criteria, histiocytosis is divided into several clinical stages, with category I signifying low risk of multifocal histiocytosis, category II and III denoting moderately aggressive multifocal histiocytoses related to scores 1 and 2, respectively, and category IV comprising multifocal aggressive histiocytoses such as Letterer-Siwe disease, i.e., score 3 [3].

Case report

A 43-year-old overweight female patient was admitted to the clinic due to front neck pain and swelling accompanied by fatigue and malaise that have persisted for two months without febrile episodes or local signs of inflammation. The patient was unaware of any other ailments and had regular menstrual cycles. Her medical history revealed uterine cervical conization, pathohistologically (PH): cervical intraepithelial neoplasia (CIN)2 (high grade squamous intraepithelial lesion – H-Sil) and CIN1 (low grade squamous intraepithelial lesion – L-Sil), and obesity, along with the family history of thyroid disease, breast malignancy, lung malignancy, cardiovascular pathology, and obesity. During the physical examination, the patient did not exhibit any alterations in the state of consciousness or orientation and was afebrile, with a normal respiratory rate at rest, but was cyanotic without evident peripheral lymphadenopathy.

No visible pathological venous or arterial pulsations were present on neck examination, but further assessments revealed an enlarged and extremely firm right thyroid lobe that was excessively sensitive to palpation. The thorax was cylindrical and respiratory movements were normal. Auscultation revealed normal breath sounds without accompanying pathological phenomena; arterial tension was 120/75 mmHg, and electrocardiography (ECG) recorded sinus rhythm, with a frequency of 70 beats per minute, and nonspecific changes of ST segments and T wave, without rhythm and conduction disturbances. The abdomen was soft and insensitive to palpation; the liver was of normal size and consistency; the spleen was nonpalpable, while renal percussion was negative on both sides. No edemas or varicose veins were visible in the extremities, and the dorsal pedal pulses were symmetrically palpable. After the examination, an ultrasound of the thyroid gland was performed, and surgical treatment was advised, along with additional diagnostics, fine-needle aspiration biopsy (FNAB) of the right thyroid lobe under ultrasound control.

Except for pathological values of thyroid-stimulating hormone (TSH): 11.7 uIU/mL [reference range (RR) 0.27–4.20 uIU/mL], adrenocorticotropic hormone (ACTH): 30.7 pg/mL (RR < 15 pg/mL), anti-thyroid peroxidase (anti-TPO) antibodies > 1,000 IU/mL (RR < 34 IU/mL), and anti-thyroglobulin (anti-TG) antibodies: 122.0 IU/mL (RR < 115 IU/mL), other blood test results (complete blood count, biochemistry) were within their respective RRs. The control ACTH value was within the RR – 10.5 pg/mL.

Echosonographic findings of the thyroid gland (Figure 1 A–D) pointed to the enlarged right thyroid gland lobe, insufficiently demarcated from the surrounding tissues. It was characterized by pronounced parenchyma inhomogeneity, reduced echogenicity of the anterior, and pronounced hypoechogenicity of the posterior region, permeated with fibrous bands and calcifications The left thyroid gland lobe exhibited pseudonodular formations indicative of a chronic inflammatory process.

A fine needle biopsy (FNB) findings corresponded to atypia of undetermined significance (AUS) with the presence of lymphocytic thyroiditis according to the Bethesda classification (hypercellular smear, lymphocytes, Hurthle cells, nuclear overlap, anisocytosis, anisonucleosis, and the presence of nuclear incisions). In accordance with the cytological examination results, the patient was referred for surgical intervention, which was uneventful, with a favorable postoperative course.

FNAB was of exceptional importance. It was performed after the first clinical examination, followed by surgical treatment, PH verification, and additional immunohistochemistry, and thus the diagnosis of an early phase of histiocytosis (unifocal). Following the diagnosis and surgical treatment, L-thyroxine treatment was continued as a substitutional therapy for post-surgical hypothyroidism, with constant and systematic monitoring of the pathological and clinical course of histiocytosis.

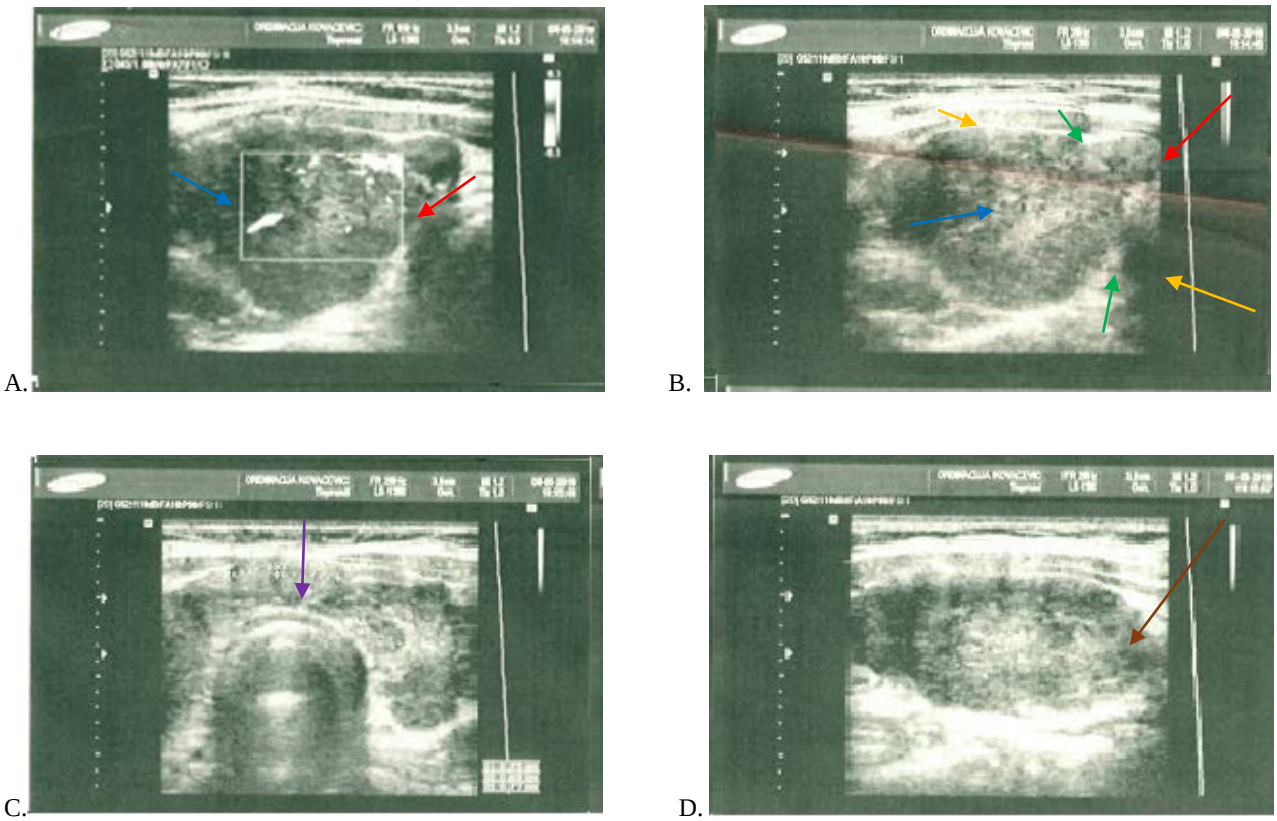

Fig. 1 – An echocardiogram of the thyroid gland: A) and B) the right lobe (indicated by red arrows); the right lobe has unclear boundaries (yellow arrows) from the surrounding tissue, heteroechogenic parenchyma with pronounced hypoechogenicity (marked with blue arrows) and calcifications (marked with green arrows) in the posterior aspect; C) The isthmic part (indicated by purple arrow); D) The left lobe (indicated by brown arrow) is pseudonodularly altered.

However, as PH findings corresponded to the fibrous form of chronic thyroiditis (Figures 2–4), the monoclonal proliferation of histiocyte and/or lymphoid cells could not be ruled out; hence, additional IH examination was indicated.

IH findings corresponded to Hashimoto's thyroiditis and LC tumor, i.e., histiocytosis. Regarding IH findings, LCs showed positive staining of S-100 protein and CD1a, whereby their negative reaction to cytokeratins, thyroglobulin, and TTF1 helped distinguish LCH from epithelial neoplasms of the thyroid gland (Figures 5–7).

In some cases, the infiltrative nature of these cells may indicate the proliferation of hematopoietic cells. Leukemias and lymphomas are diagnosed differently, and although LCs often exhibit poor diffuse LCA (CD45) staining, B and T lymphocyte markers are negative in the case of LCH. Even though S-100 positivity may raise suspicion of melanoma, LCs show negative staining of very specific melanoma markers such as HBM-45 and MART-1.

The final diagnosis was established as follows: tumor affecting the right thyroid gland lobe, autoimmune chronic thyroiditis, and primary hypothyreosis.

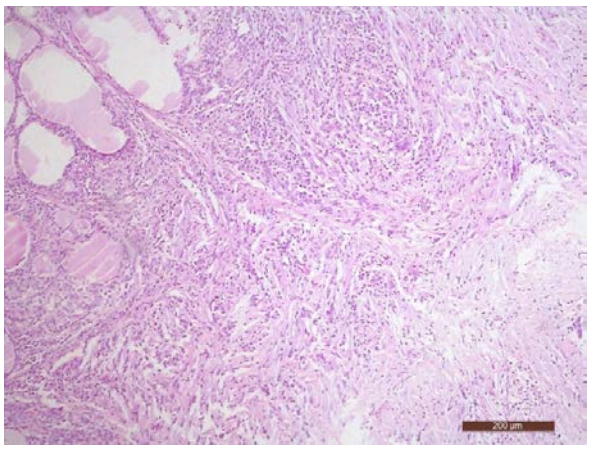

Fig. 2 – Reduced glandular tissue of thyroid gland with signs of oxyphilic metaplasia (hematoxylin and eosin staining, ×50).

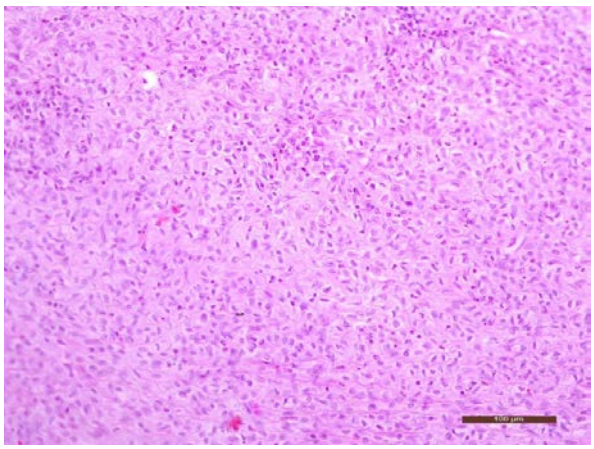

Fig. 3 – Langerhans cell (LC) histiocytosis composed of characteristic reniform irregular-border LC with interspersed eosinophils (hematoxylin and eosin staining, ×400).

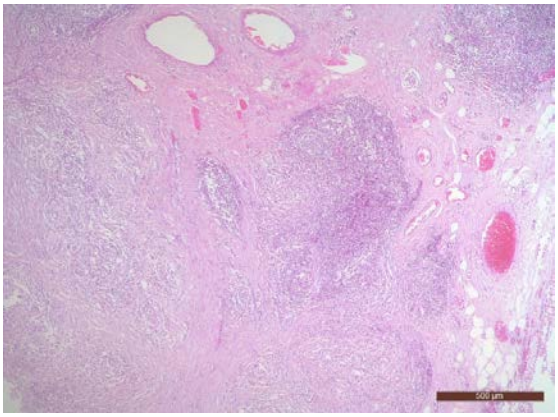

Fig. 4 – Langerhans cell histiocytosis stroma with signs of fibrosis, dense lymphocytic infiltrate, and formation of lymphoid follicles (hematoxylin and eosin staining, ×200).

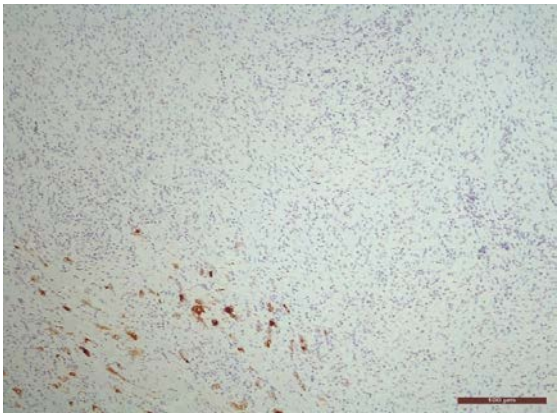

Fig. 5 – Lack of thyroglobulin expression in Langerhans cell histiocytes, with few entrapped thyrocytes that are positive for the applied immunohistochemical (IH) marker (thyroglobulin IH staining, ×200).

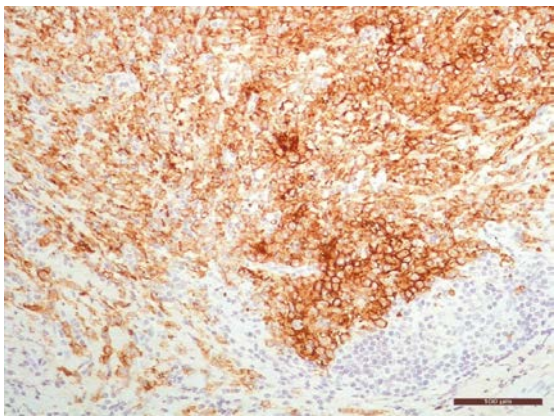

Fig. 6 – Diffuse and strong positivity of CD1a marker in Langerhans cells, with lack of expression for the applied marker in surrounding lymphocytes and thyrocytes (CD1a immunohistochemical staining, ×200).

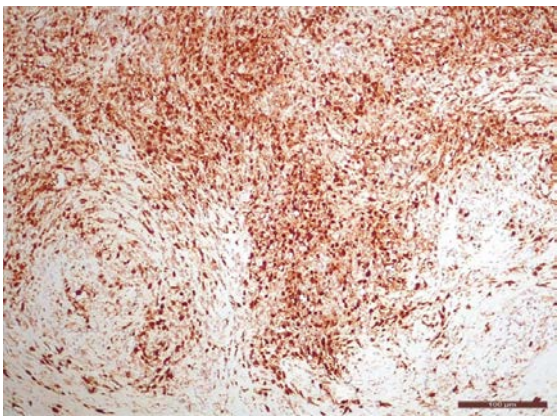

Fig. 7 – Positive expression of S-100 protein in Langerhans cells, with the lack of immunoreactivity of surrounding thyrocytes and lymphocytes (S-100 immunohistochemical staining, ×200).

The therapy ordered was L-thyroxine (Euthyrox) 100 μg tablet daily.

Guided by the IH findings, since histiocytosis may be a multifocal disease, in addition to commencing L-thyroxine replacement therapy, the patient underwent an additional functional examination of the pituitary gland along with an oncological examination.

Laboratory findings six months after the surgery and histiocytosis diagnosis showed normal values of leukocytes, hemoglobin, mean corpuscular volume, and platelets. Hormonal status showed normal values of follicle-stimulating hormone, luteinizing hormone, prolactin, ACTH, cortisol, TSH, and free thyroxine due to L-thyroxine therapy.

Chest computed tomography (CT) after surgery revealed the presence of three cystic changes in the lung parenchyma on the right side and one micronodule 4 mm in diameter in both lobes.

Abdominal and pelvic CT showed normal findings without any signs of pathological changes.

Follow-up examination 10 months after surgical treatment showed normal abdominal ultrasound findings, with biochemical markers within their respective reference values. A 6-month follow-up was scheduled, along with regular five-year-long monitoring by oncologists and endocrinologists.

Discussion

LCH lesions comprise large histiocytes with abundant cytoplasm and eosinophils, along with the proliferation of mononuclear DC with local and diffuse infiltration. Infiltrates are most commonly found in bone marrow, bones, lungs, endocrine glands, liver, and skin. LCs are characterized by rod-like cytoplasmic organelles (Birbeck granules), the so-called DC, expressing surface glycoproteins (CD11) and langerin (CD207), both of which are bound to the major histocompatibility complex of classes 1 and 2 [4]. LCH cells also possess Birbeck granules, but differ in shape from LCs in that they are rounded and have no dendritic extensions, and express CD1a, CD207, and S-100 proteins at the molecular level, but do not express markers that possess mature DC, such as CD83 [5]. More than 50% of cases involve *BRAF* mutations [6].

It has been considered that the *BRAF* V600E mutation in LCH could lead to papillary thyroid carcinoma by creating

a microenvironment that is appropriate for neoplastic transformation [7]. Most mutations activate signaling enzymes that result in the activation of extracellular signals by kinase. Given the significant clinical responses to the use of rapidly accelerated fibrosarcoma family inhibitors in patients with LCH and *BRAF* mutations, these mutations are likely authentic disease drivers in LCH. The *BRAF* mutation stimulates *via* RAS/RAF/MEK/ERK signaling pathway, which leads to constitutive transcription of genes involved in different cellular responses. Although histiocytosis mainly affects children and is mostly multisystemic, it also occurs in adults and can be isolated or multifocal. Only a small number of cases have been described in the literature, mostly pertaining to isolated thyroid gland histiocytosis [8, 9], which is associated with nearly 100% survival [10]. FNAB of the thyroid gland is crucial in cytological diagnosis, as it contributes to the distinction between benign and malignant processes in the distorted structure of the thyroid gland. Diagnostic puncture of the unusually altered thyroid gland, as well as parts affected by autoimmune disease, provides important information related to rare pathological changes in thyroid cells. Some cytomorphologic features of the LCH may be associated with thyroid diseases such as chronic lymphocytic thyroiditis and papillary thyroid cancer.

It typically affects bones, lungs, skin, hypothalamus, and the posterior thyroid gland lobe. Physical examination usually reveals an enlarged thyroid gland, as was the case with our patient. Although elevated antithyroglobulin antibodies are typically reported in the literature, antithyroid antibodies may also be elevated, as in our case. In some patients, LCH was initially misdiagnosed as poorly differentiated thyroid carcinoma. On the other hand, several authors noted an association between LCH and thyroid cancer in adults [11–13]. Compared to pituitary involvement, thyroid LCH is much rarer and usually occurs in adults. Thyroid function can be in the euthyroid range or be indicative of primary hypothyroidism, as in our case [14]. Most adults diagnosed with isolated thyroid LCH are only treated surgically, even though chemo- and radiotherapy can also be advised in some cases. The most optimal therapy mode is determined based on the disease severity and progression, i.e., involvement of high- or low-risk organs. Therapeutic options include conservative follow-up therapy, hormone substitution, cytokine inhibitors, organ transplantation, and stem cell therapy [15–17].

Cases of histiocytosis in the lungs that have been previously reported mainly indicated solitary localization, with a prevalence of 1 in 200,000 [18]. For our patient, continued monitoring was required, as lung CT revealed three cystic changes on the right side of the lung parenchyma. In adults, LCH with orbital histiocytosis is rare. Bermingham et al. [19] described a 45-year-old man with a right medial node that persisted for five weeks and a patient in whom a biopsy of the lesion showed histiocytic cells, basophils and LCs, posterior uveitis, vasculitis, and neurological symptoms stemming from the presence of LCH cells in the cerebrospinal fluid [20]. Chronic autoimmune thyroiditis is the most common cause of acquired primary hypothyroidism. It has an autoimmune etiology in which heredity plays a role. Moreover, autoimmunity has been proven based on PH findings of diffuse lymphocytic infiltration of the thyroid gland. It is an aberrant expression of class II major histocompatibility complex molecules, which present the antigen to CD4 T lymphocytes specific for thyroid antigens. The disease is eight times more common in women than men, and its incidence increases with age.

Conclusion

Histiocytosis is a rare disease, especially in adulthood, but autoimmune thyroid disease is quite common in adolescents as well as adults. Therefore, it is essential to take a detailed medical history and conduct a thorough clinical examination during the patient's first visit and consider histiocytosis in the differential diagnosis of autoimmune thyroid disease. Furthermore, unusual clinical presentation and/or ultrasound features of autoimmune thyroiditis should lead to prompt FNB and additional IH examination (when medically indicated).

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