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ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

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THE IMPACT OF ABDOMINAL AORTIC ANEURYSM DIAMETER ON THE OUTCOME OF ENDOVASCULAR AORTIC REPAIR

UTICAJ VELIČINE ANEURIZME ABDOMINALNE AORTE NA ISHOD ENDOVASKULARNE REPARACIJE AORTE

Nikola BATINIĆ[1, 2], Tijana KOKOVIĆ[3], Dragan NIKOLIĆ[1, 4], Vladimir MANOJLOVIĆ[1, 2], Viktor TILL[1, 3] and Slavko BUDINSKI[1, 2]

Summary

Introduction. Abdominal aortic aneurysm diameter is one of the most important parameters in the diagnostic and therapeutic algorithm for aneurysm follow-up. Currently, two therapeutic modalities are used: open surgery and endovascular aortic repair. The aim of this study is to analyze the impact of the maximum transverse diameter of the abdominal aortic aneurysm on the incidence of general and specific complications. **Material and Methods.** The retrospective study included 75 patients with infrarenal abdominal aortic aneurysm who underwent endovascular aortic repair in the period from July 2008 to January 2020. The patients were divided into two groups: group A with an abdominal aortic aneurysm size ≤ 5.9 cm, and group B with an abdominal aortic aneurysm size ≥ 6.0 cm. **Results.** A total of 41.3% of patients presented with a maximum transverse aneurysm diameter of ≤ 5.9 cm, and 58.7% of patients had ≥ 6.0 cm. Of comorbid diseases, chronic obstructive pulmonary disease was more prevalent in patients with a large abdominal aortic aneurysm (group A 25.8%; group B 59.1%). None of the other comorbidities showed a statistically significant difference between the two groups of patients. Early complications were present in a total of 14.7% of patients, of which 12.9% of patients with a small and 15.9% with a large abdominal aortic aneurysm. Late complications occurred in a total of 18.7% of patients, in 9.7% of patients with a small and 25% of patients with a large abdominal aortic aneurysm. **Conclusion.** Patients with abdominal aortic aneurysms with a maximum transverse diameter of 6 cm and larger, present with a higher rate of late postoperative complications, increase in aneurysmal sac on control multislice computed tomography angiography, and have a worse prognosis compared to patients with smaller abdominal aortic aneurysms.

Key words: Aortic Aneurysm, Abdominal; Diagnosis; Endovascular Procedures; Postoperative Complications; Treatment Outcome; Risk Factors; Prognosis; Comorbidity

Sažetak

Uvod. Dijametar aneurizme abdominalne aorte jedan je od najbitnijih parametara za dijagnostički i terapijski algoritam praćenja aneurizme. Trenutno se koriste dva terapijska modaliteta – otvoren hirurški tretman i endovaskularni tretman. Cilj studije je analiza uticaja maksimalnog poprečnog dijametra aneurizme abdominalne aorte na pojavu opštih i specifičnih komplikacija. **Materijal i metode.** Retrospektivnom studijom je obuhvaćeno 75 bolesnika sa infrarenalnom aneurizmom abdominalne aorte, koji su u periodu od jula 2008. do januara 2020. godine tretirani endovaskularnom reparacijom aorte procedurom. Pacijente smo podelili u dve grupe: grupa A sa veličinom aneurizme abdominalne aorte ≤ 5,9 cm i grupu B sa veličinom aneurizme abdominalne aorte ≥ 6 cm. **Rezultati.** Maksimalni poprečni dijametar ≤ 5,9 cm imalo je 41,3% pacijenata, a 58,7% pacijenata je imalo dijametar ≥ 6 cm. Od pridruženih bolesti, hronična opstruktivna bolest pluća je zastupljenija kod pacijenata sa velikom aneurizmom abdominalne aorte (grupa A 25,8%; grupa B 59,1%). Nijedan od ostalih komorbiditeta nije pokazao statistički značajnu razliku između dve grupe pacijenata. Rane komplikacije su se javile kod ukupno 14,7% pacijenata, od toga kod 12,9% pacijenata sa malom i 15,9% pacijenata sa velikom aneurizmom abdominalne aorte. Kasne komplikacije su se javile kod ukupno 18,7% pacijenata, i to kod 9,7% pacijenata sa malom i 25% pacijenata sa velikom aneurizmom abdominalne aorte. **Zaključak.** Pacijenti sa aneurizmom abdominalne aorte čiji je maksimalni poprečni dijametar 6 cm i više, imaju veći procenat kasnih postoperativnih komplikacija, kao i porasta aneurizmatskog sakusa na kontrolnoj multislajs kompjuterizovanom tomografskoj angiografiji, te imaju lošiju prognozu u odnosu na pacijente sa manjom aneurizmom abdominalne aorte.

Ključne reči: aneurizma abdominalne aorte; dijagnoza; endovaskularne procedure; postoperativne komplikacije; ishod lečenja; faktori rizika; prognoza; komorbiditet

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Abbreviations

AAA – abdominal aortic aneurysm
EVAR – endovascular aortic repair
HTA – arterial hypertension
COPD – chronic obstructive pulmonary disease
MSCTA – multislice computed tomography angiography
DSA – digital subtraction angiography

Introduction

An aneurysm is a permanent, concentric or eccentric, segmental dilatation in the wall of an artery, at least 1.5 times its normal diameter [1]. Today, in clinical practice, an aneurysm of the infrarenal abdominal aorta is defined as a dilatation with a diameter of 3 cm in men and 2.7 cm in women [2].

The aortic aneurysm is a disease predominantly affecting the elderly population. The incidence of aortic aneurysm increases after the age of fifty. It is three to six times more common in males, and the most common etiological factor is medial degeneration, due to atherosclerotic processes [3, 4].

The annual risk of aneurysm rupture directly depends on the size of the aortic aneurysm, and therefore the diameter of the aneurysm is one of the most important parameters in the diagnostic and therapeutic algorithm for its monitoring. The annual risk of rupture of abdominal aortic aneurysms (AAA) with a diameter of 3 to 3.9 cm is 0.3%; in aneurysms with a diameter of 4 to 4.9 cm it is 0.5 – 1.5%; in 5 to 5 .9 cm diameter aneurysms the risk is 1 – 11%, in 6 – 6.9 cm diameter aneurysms it is 11 – 22%, and in aneurysms with a diameter over 7 cm the risk is more than 30% [5]. In addition to the diameter of the aneurysm, the aneurysm rupture prediction includes the growth rate of the aneurysm and the increase in the thickness of the thrombus in the aneurysmal sac. An increase in AAA diameter over 7 mm in 6 months, or greater than 10 mm in one year is an indication for surgery, regardless of its diameter [6]. Apart from the above parameters, some are important in treatment decisions. When making a decision, it is necessary to take into account the individual risk for each patient, the surgical risk, and the age of the patient [1, 7].

Currently, two therapeutic modalities are used in the treatment of AAA:

1. Open surgical treatment;
2. Endovascular aortic repair (EVAR).

Although endovascular treatment has become a complement to open surgical treatment, its role must be clearly defined in each patient. Criteria for infrarenal endograft placement are clearly defined. In general, in the treatment of aortic aneurysms, the endovascular procedure is primarily indicated in the elderly, high-risk patients, or patients with contraindications for open surgery. The main advantage of this method over open surgery is lower postoperative mortality, while the percentage of reinterventions is significantly higher compared to open surgery [8, 9].

Complications that may occur after EVAR are divided into general and specific, as well as early and late. Specific complications can be divided into procedure-related complications and endograft-related complications, such as endograft migration, endograft thrombosis, stenosis, endograft kinking, and endoleaks.

Although patients with smaller AAAs are known to have a better early and late outcome after EVAR compared to patients with larger aneurysms, the relationship between a large aneurysm and EVAR outcome is still not completely clear. Several retrospective studies have shown that EVAR has a better outcome in patients with a smaller AAA, compared to patients with larger aneurysms [10–12].

The aim of this study is to analyze the impact of the maximum transverse diameter of the AAA on the incidence of general and specific complications, such as endoleaks, graft thrombosis, increase in diameter, and rupture of the AAA during EVAR.

Material and Methods

The retrospective study included 75 patients with infrarenal AAA, who were treated with EVAR in the period from July 2008 to January 2020, at the Radiology Center of the Clinical Center of Vojvodina, Serbia.

Prior to the intervention, all patients underwent multislice computed tomography angiography (MSCTA), based on which sizing and planning of EVAR were performed according to the manufacturer's use instructions for the endoprosthesis. All examinations were performed using Siemens Somatom Emotion 16, Siemens Somatom Sensation 64 and Siemens Sensation 128 CT scanners. The anterior-posterior, latero-lateral, and cranio-caudal diameters of the aneurysm neck and aneurysmal sac were measured in all three planes (axial, coronal, and sagittal).

The following parameters were collected preprocedurally: sex and age, size and shape of AAA, associated diseases, arterial hypertension (HTA), cardiomyopathy, chronic obstructive pulmonary disease (COPD), hyperlipoproteinemia, diabetes mellitus, renal failure, as well as cigarette use.

All interventions were performed in an angiography room equipped with Axiom Artis (Siemens) system with a C-port and flat-panel detector, and a software package that provides digital subtraction angiography (DSA) with a roadmapping option. Interventions were performed under general endotracheal anesthesia, by direct access through previously surgically prepared femoral arteries.

After each intervention, a control DSA was performed to check the position of the graft and potential complications. Medtronic grafts were used in all patients - Talent, Endurant, Endurant II, and Endurant IIC.

Control MSCTAs were performed after 1, 6, and 12 months in the first postoperative year, and then once a year. In our research, the follow up period was from 1 to 11 years.

Early and late post-procedural complications were monitored, as well as endoleaks as specific complications, on control DSA and MSCTA, endoleak closure, increase in aneurysm size (on control MSCTA after 12 months), and duration of hospital stay. To analyze the results of EVAR, data from medical histories, data from

the endovascular procedure protocol, as well as data from MSCTA findings were used, with the informed consent of each patient.

To determine the effects of aneurysm size on EVAR outcome, the patients were divided into two groups: group A with an AAA size of 5.9 cm or less, and group B with an AAA size of 6 cm or larger. All the obtained data were entered into a table and statistically processed. The following parameters were determined: total value, mean value, and standard deviation. The Pearson χ^2 test was used to compare these two groups.

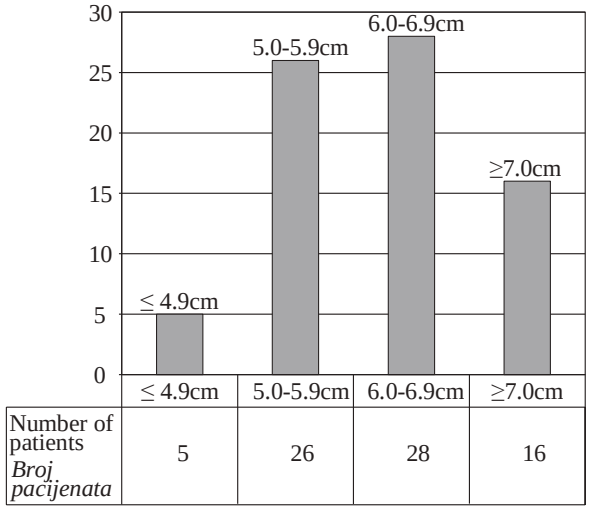
Results

The study included 75 patients with infrarenal AAA; 31/75 (41.3%) patients had a maximum transverse aneurysm diameter ≤ 5.9 cm, and 44/75 (58.7%) patients had a transverse diameter ≥ 6.0 cm. The average size of AAA was 6.46 cm (the smallest AAA was 4.7 cm and the largest 8.3 cm). The distribution of patients by transverse AAA diameter (size) is shown in **Graph 1**.

The main characteristics of patients with a small AAA diameter (group A ≤ 5.9 cm) and those with a large diameter (group B ≥ 6.0 cm) are listed in **Table 1**. In both groups, there were more male patients (group A 29/31 – 93.5% and group B 41/44 – 93.1%). The average age of patients was slightly higher in those with a large aneurysm (group A 68.2 years, group B 75.7 years). The oldest patient was 87 years old, and the youngest was 47 years old.

Of the associated diseases, COPD was more prevalent in patients with a large AAA compared to patients with a small AAA (group A 8/31 – 25.8%; group B 26/44 – 59.1%). None of the other comorbidities showed a statistically significant difference between the two groups of patients, while the most common comorbidity in both groups was hypertension (group A 25/31 - 80.6%; group B 36/44 – 81.8%).

Fusiform aneurysms were more common in both groups compared to saccular aneurysms, in group A 28/31 (90.3%) and group B 39/44 (88.6%).



Graph 1. Distribution of patients by transverse AAA diameter

Grafikon 1. *Distribucija pacijenata prema poprečnom dijametru aneurizmom abdominalne aorte*

The EVAR was performed as planned in all patients, without conversion to open surgery, except for one patient from group A, who underwent femoro-femoral crossover bypass grafting due to the impossibility of arm dilatation.

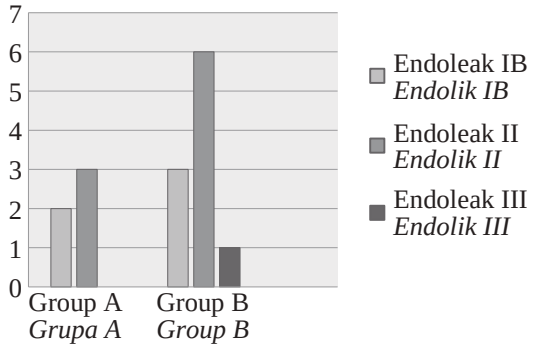
The length of hospital stay after EVAR showed no statistically significant difference - Group A 5.72 (4 – 14) and Group B 5.88 days (4 – 15).

As a specific complication, early endoleak occurred on control DSA in 15/75 patients (20%); in 5 patients with a small AAA (5/31 – 16.1%) and 10 with a large AAA (10/44 – 22.7%). There was no statistically significant difference between the two groups (p = 0.157). The following endoleaks have been described: Group A - Type IB 2/31 (6.5%); Type II 3/31 (9.7%), while there were no endoleaks type IA, III, IV and V. In Group B, the following types were found: Type IB 3/44 (6.8%); Type II 6/44 (13.6%) and Type III 1/44 (2.3%).

Table 1. Gender, age and comorbidity distribution of patients with AAA

Tabela 1. *Distribucija prema polu i godinama i komorbiditeti pacijenata sa aneurizmom abdominalne aorte (AAA)*

	Group A (AAA ≤ 5.9 cm) *Grupa A (AAA ≤ 5.9 cm)*	Group B (AAA ≥ 6.0 cm) *Grupa B (AAA ≥ 6.0 cm)*	p *p*
Number of patients/*Broj pacijenata*	31	44	–
Male/*Muški pol*	935% (29/31)	93.1% (41/44)	0.959
Average age/*Prosečna starost*	68.2 (57 – 77) SD 5,7879	75.7 (47 – 87) SD 12,0746	0.000249
Hypertension/*Hipertenzija*	80.6% (25/31)	81.8% (36/44)	0.90
Hyperlipoproteinemia/*Hiperlipoproteinemija*	22.6% (7/31)	15.9% (7/44)	0.8602
Chronic obstructive pulmonary disease *Hronična opstruktivna bolest pluća*	25.8% (8/31)	59.1% (26/44)	0.000835
Diabetes mellitus/*Šećerna bolest*	22.6% (7/31)	31.8% (14/44)	0.4781
Cardiomyopathy/*Kardiomiopatija*	45.1% (14/31)	45.4% (20/44)	0.6563
Cigarette use/*Pušenje*	48.4% (15/31)	45.4% (20/44)	0.704
Renal failure/*Bubrežna slabost*	9.7% (3/31)	9.1% (4/44)	0.527
Fusiform aneurysm/*Fuziformna aneurizma*	90.3% (28/31)	88.6% (39/44)	0.649



Graph 2. Types of endoleaks on control digital subtraction angiography
Grafikon 2. *Tip endolika na kontrolnoj digitalnoj suptrakcionoj angiografiji*

The endoleak types on control DSA are shown in **Graph 2**.

The mean time between the EVAR and endoleak closure on control MSCTA was 9 months and it was the same in both groups (group A 8.4 and group B 9.6 months). The shortest endoleak closure was after one month, and the longest after 24 months.

Early complications were present in 11/75 patients (14.7%), of which 4 patients with a small AAA (Group A 12.9%) and 7 with a large AAA (15.9%). Early complication that occurred within the first 30 days after surgery was found in 6 patients, of which in two patients with a small AAA and in 4 patients with a large AAA. Local wound complications occurred in 2 patients, one patient from each group. One patient from group A was diagnosed with acute lower limb ischemia and underwent urgent autovenous femoro-popliteal bypass surgery. Graft kinking occurred in two cases. One patient had a non-significant right common iliac artery stenosis (30 – 40%). Another patient developed endograft thrombosis and occlusion of the right common iliac artery. On the third postoperative day, the patient developed symptoms of ischemia of the right lower extremity, with acute claudication, without rest pain, and a normal neurological finding. Since there were no signs of critical ischemia, further conservative treatment was continued. Both patients were from group B, with a large AAA **(Table 2)**.

Late complications occurred in 14/75 patients (18.7%); 3 patients with a small AAA (9.7%) and 11 patients with a large AAA (25%). Graft limb thrombosis occurred in 4 patients, 2 from each group. All of them underwent extra-anatomical crossover femoro-femoral bypass surgery due to critical ischemia. During the follow-up, MSCTA was performed 12 months after EVAR, showing aneurysm growth of more than 5 mm in 8 patients, one patient with a small AAA and 7 patients with a large AAA. There were two patients with AAA rupture and both were from the group B with a large AAA. In the first patient, the rupture occurred three years after EVAR. The patient underwent urgent surgery with aneurysmectomy and tube graft interposition. The patient was discharged on the seventh postoperative day for further home treatment. In another patient, AAA rupture occurred 9 years after EVAR. One year after the endovascular intervention, the patient still had type II endoleak on control MSCTA. He was conservatively treated since he was asymptomatic and did not have an increase in the maximum transverse diameter. After the diagnosis, he underwent urgent reoperation with aneurysmectomy and tube graft interposition, but the patient passed away on the twentieth postoperative day. Two patients from group B with a large AAA had endograft migration, and one underwent REDO endovascular procedure. Due to the symptomatology and expansion of the aneurysmal sac another patient underwent open surgical treatment with aneurysmectomy and tube graft interposition.

Table 2. Comparative analysis of postoperatively monitored parameters
Tabela 2. *Komparativna statistika parametara praćenih postoperativno*

	Group A ≤ 5.9 cm *Grupa A ≤ 5.9 cm*	Group B ≥ 6.0cm *Grupa B ≥ 6.0 cm*	p *p*
Endoleak on DSA/*Endolik na DSA*	16.1% (5/31)	22.7% (10/44)	0.1135
Closure of endoleak *Zatvaranje endolika*	8.4 mounths (1 - 12) SD 4,7644	9.6 mounths (1 - 24) SD 8,2811	0.484
Conversion to open surgery/*Konvertovanje u otvorenu hirurgiju*	3.2% (1/31)	0% (0/44)	0.388
Early complications/*Rane komplikacije*	12.9% (4/31)	15.9% (7/44)	0.125
Late complications/*Kasne komplikacije*	9.7% (3/31)	25% (11/44)	0.0041
Increase of AAAA transverse diameter more than 5 mm - 12 mounth after EVAR/*Povećanje poprečnog dijametra AAA preko 5 mm 12 meseci nakon EVAR-a*	3.2% (1/31)	18.2% (8/44)	0.0022
Lower limb thrombosis/*Tromboza donjih ekstremiteta*	6.5% (2/31)	4.5% (2/44)	0.125
Rupture of AAA/*Ruptura AAA*	0% (0/31)	4.5% (2/44)	0.095
Graft migration/*Migracija grafta*	0% (0/31)	4.5% (2/44)	0.095
Length of hospital stay (days)/*Dužina hospitalizacije (dani)*	5.72 SD 2,7706	5.88 SD 2,8353	0.410

Legenda: DSA – digitalna suptrakciona angiografija; AAA – aneurizma abdominalne aorte; EVAR – endovaskularni tretman AAA (aneurizme abdominalne aorte)

Discussion

Aortic aneurysm disease is the 9th leading cause of death in people over 65 years of age, and the 13th leading cause of death in general [13]. According to the National Center for Health Statistics, the number of patients with AAA has increased by as much as 300% in the past 30 years, with a tendency to further increase [14]. The increase in the number of newly diagnosed patients is explained by the fact that more modern diagnostic procedures (ultrasound, MSCTA, magnetic resonance angiography) are now available, as well as the extension of life expectancy in general. In Serbia, between 700 and 800 patients with AAA are diagnosed annually, while the number of patients who undergo aneurysm reconstruction is about 500 [15].

The epidemiological data obtained in the study show a significantly higher number of males (group A 93.5%, group B 93.1%), which is in line with the literature data [11–14]. The study showed that patients with a small AAA, who were classified in group A, are significantly younger than patients with a large AAA (group A 68.2 years, group B 75.7). This corresponds to previously known data in the literature claiming that AAA is a disease of the elderly population and that the risk increases with age [3, 11, 12].

Of the associated diseases that we monitored, the most common was HTA (group A 80.6%, group B 81.8%), cardiomyopathy (group A 45.1%, group B 45.4%), as well as cigarette use (group A 48.4%, group B 45.4%). In addition to these comorbidities, all others showed equal distribution among patients of both groups, which is in line with the literature [10, 11, 16]. In our study, only COPD was significantly more prevalent in patients with a large AAA. The obtained results are in accordance with the literature data showing that atherosclerotic changes and cardiovascular diseases are the most common comorbidities among patients with aortic aneurysm disease [17]. Jones W. et al. [11], found a lower prevalence of comorbidities in patients with a small AAA, which can be explained by the selection of patients.

According to the literature, fusiform AAA is the most common anatomical type [3] and it corresponds to the results obtained in our study (group A 90.3%, group B 88.6%). Endovascular intervention was performed as planned in all patients, without conversion to open surgery. Only one patient underwent femorofemoral crossover bypass grafting, which speaks in favor of good preoperative preparation of patients in our study and adequate preoperative diagnosis, as well as a good technique.

The average hospital stay is in line with data from the literature [18], 3 to 6 days on average. The study did not show a significant difference between patients with a large and small AAA; group A 5.72 (4 – 13) and group B 5.88 days (4 – 14).

Endoleaks are the most common complication after EVAR. They are the passage of blood into the aneurysmal sac after the endovascular procedure and there are 5 types of endoleaks [19, 20]. On control intraoperative DSA, endoleaks were found in 20% (12/75) of patients, which is slightly less than the expected percentage of about 25% reported in the literature [1, 21]. Endoleaks did not show a statistically significant difference between the two groups (group A 16.1% 5/31; group B 22.7% 10/44). The most common type of endoleak in both groups was type II, in patients with a large AAA in 13.6% (6/44), while in patients with a small AAA it was present in 9.7% of cases (3/31). The obtained results are in agreement with the literature results, where endoleak type II is also the most common [14, 15]. The average endoleak closure period on control MSCTA examinations was 9 months (maximum 24 months, minimum 1 month). In two patients, no endoleak closure occurred after 24 months. Both presented with endoleak type II and were from group B with a large AAA. Neither of these two patients required reintervention, as they were asymptomatic and neither had an increase in AAA diameter greater than 5 mm, which is consistent with literature data [1, 22, 23].

Early complications showed an equal distribution among patients with a large and small AAA (group A 12.9%, group B 15.9%). They included mostly local complications such as infection, surgical wound hematomas, as well as fever, and were of no great clinical significance. One patient developed acute lower limb ischemia and underwent urgent autovenous femoropopliteal bypass surgery. Graft kinking occurred in two patients, but they did not need a surgical treatment. The incidence of these complications is consistent with the literature data [18].

Late complications were more common in patients with a large AAA (group A 9.7%, group B 25%). Endovascular AAA treatment is considered to be successful if the diameter of the aortic aneurysm has not increased more than 5 mm after one year on control MSCTA compared to the preoperative finding [24, 25]. Our research showed that the percentage of patients with an increase in AAA diameter greater than 5 mm on control MSCTA 12 months after EVAR was statistically significantly higher in group B, patients with a large AAA (group A 3.2% 1/31; group B 18, 2% 8/44). This corresponds with the results obtained by Jim et al. [11] as well as Jones et al. [11]. Except for the increase in the maximum transverse AAA diameter, other complications did not show a statistically significant difference. Lower limb graft thrombosis occurred in 4 patients and all of them underwent surgical treatment with extra-anatomical crossover femoral-femoral bypass. A rupture of AAA was found in two patients and both were surgically treated with aneurysmectomy and tube graft interposition. The overall percentage of complications in our study is slightly lower than in the available literature [1], while the prevalence of late complications in patients with a large AAA corresponds with literature data [10, 11]. A lower incidence of total complications may be explained by the selection of patients. Our study included only patients with asymptomatic AAA, who were at high risk for open surgery due to comorbidities. All patients had previously undergone adequate preoperative preparation and all fulfilled the clearly defined criteria for EVAR as recommended by the manufac-

turer. Several studies have already shown good results in terms of high levels of technical success as well as low morbidity of EVAR in patients at high risk for open surgery [26–28].

Conclusion

Patients with abdominal aortic aneurysms with a maximum transverse diameter of 6 cm and larger present with a higher rate of late postoperative complications, increase in aneurysmal sac on control multislice computed tomography angiography, and have a worse prognosis compared to patients with smaller abdominal aortic aneurysms. The obtained results indicate that the maximum transverse diameter of the aneurysm is an important prognostic parameter in planning endovascular procedures.

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THE IMPACT OF BODY MASS INDEX ON THE RESULTS OF ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

UTICAJ INDEKSA TELESNE MASE NA REZULTAT REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA

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Summary

Introduction. The aim of the study was to determine the quality of life among groups with different body mass index after anterior cruciate ligament reconstruction. **Material and Methods**. The study included 510 patients who underwent surgery 95% were athletes, 81% were males, with an average age of 27 years. The body mass index was calculated for all patients, and the quality of life was evaluated using the Knee Osteoarthritis Outcome Score. **Results and Discussion**. The mean body mass index was 24.65, with the highest percentage of normal weight athletes (59%). The body mass index is inversely proportional to the Knee Osteoarthritis Outcome Score, so obese patients have a poorer quality of life ($p = 0.003$). Men have a higher mean body mass index (25.21) than women (22.26). The mean body mass index increases with age, whereas recreational athletes and non-athletes have an increased mean body mass index. The correlation between the body mass index and the level of sports activity is significant, so higher body mass index is associated with lower Tegner score. The body mass index is not a significant factor for re-injury and revision reconstruction, since it does not differ significantly among patients with revision and primary anterior cruciate ligament reconstruction. The majority of patients (91.0%) rated their general health as much better than before surgery, and 67.6% of patients with an ideal body mass index thought that surgery did not affect their quality of life at all. **Conclusion**. The hypothesis that persons with increased body mass index (above 25) have a lower quality of life after anterior cruciate ligament reconstruction compared to persons with ideal body mass index (below 25) was confirmed.

Key words: Athletes; Body Mass Index; Anterior Cruciate Ligament Injuries; Anterior Cruciate Ligament Reconstruction; Quality of Life; Risk Factors; Recovery of Function; Treatment Outcome; Surveys and Questionnaires

Sažetak

Uvod. Cilj studije predstavlja utvrđivanje kvaliteta života među grupama sa različitim vrednostima indeksa telesne mase, nakon rekonstrukcije prednjeg ukrštenog ligamenta. **Materijal i metode.** U istraživanju je učestvovalo 510 operisanih pacijenata, 95% sportista, 81% muškog pola, prosečne starosti 27 godina. Svima je izračunat indeks telesne mase, a za analizu kvaliteta života korišćen je *Knee Osteoarthritis Outcome Score*. **Rezultati i diskusija.** Prosečna vrednost indeksa telesne mase iznosila je 24,65 a najveći je broj normalno uhranjenih sportista (59%). Indeks telesne mase je indirektno proporcionalan vrednostima bodovne skale korišćenog upitnika, pa gojazni pacijenti imaju lošiji kvalitet života ($p = 0,003$). Muškarci imaju prosečno viši indeks telesne mase (25,21) od žena (22,26). Godine života povećavaju prosečan indeks telesne mase. Rekreativci i nesportisti imaju povećane prosečne vrednosti indeksa telesne mase. Značajna je korelacija indeksa telesne mase sa nivoom sportske aktivnosti, pa je *Tegner* skor manji ukoliko ispitanik ima povišene vrednosti indeksa telesne mase. Indeks telesne mase ne predstavlja značajan faktor za ponovnu povredu i revizionu rekonstrukciju jer se značajno ne razlikuje među povređenima sa revizionim i primarnim rekonstrukcijama prednjeg ukrštenog ligamenta. Najveći deo (91%) pacijenata ocenio je svoje opšte zdravstveno stanje mnogo boljim nego pre operacije, a 67,6% sa idealnim indeksom telesne mase smatralo je da operisana povreda kasnije uopšte nije uticala na njihov kvalitet života. **Zaključak.** Hipoteza je potvrđena da osobe sa povećenim vrednostima indeksa telesne mase (iznad 25) imaju manje kvalitetan život nakon operacije u odnosu na osobe sa idealnim vrednostima (ispod 25).

Ključne reči: sportisti; indeks telesne mase; povrede prednjeg ukrštenog ligamenta; kvalitet života; faktori rizika; funkcionalni oporavak; ishod lečenja; ankete i upitnici

Introduction

The incidence of anterior cruciate ligament (ACL) injury in the young population is constantly increasing, especially among active athletes [1, 2]. Although it is well documented that females are at a significantly higher risk of ACL injury [1–4], the dilemmas remain: why males predominate in study samples and why does not ACL reconstruction prevent the development of osteoarthritis, especial-

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Abbreviations

ACL – anterior cruciate ligament
BMI – body mass index
SD – standard deviation
KOOS – Knee Injury and Osteoarthritis Outcome Score

ly in obese patients, since it provides knee joint stability [1, 3]. Current dilemmas are also related to the prevention of risk factors of ACL rupture [1–7], identification of the best surgical techniques with as few complications as possible [8–14], as well as the best rehabilitation protocols providing safe return to sports activities after surgery [15].

Risk factors associated with ACL injury are divided into environmental factors, hormonal, neuromuscular, biomechanical, and anatomical factors [1–4, 16, 17]. Among the anatomical factors, the most commonly mentioned are ligament laxity, quadriceps angle, knee valgus, width of the femoral intercondylar notch, and posterior tibial slope [3, 16, 17]. Body mass index (BMI) is also considered to be a potential risk factor [18] since obesity may have negative effects on health, quality of life, and postoperative recovery of patients [19].

The purpose of ACL reconstruction is not only to improve the knee function, but also to provide an optimal quality of life. Current questionnaires point to the importance of the patient's perception of his health status [7, 8, 20]. However, there is little data in the available literature on whether and how body weight, body height, and BMI affect quality of life. Therefore, we hypothesized that obesity decreases the quality of life of patients after ACL reconstruction, compared to normal weight patients; the aim of the study was to determine the quality of life among groups with different BMI after ACL reconstruction.

Material and Methods

The study was performed at the Clinic of Orthopedic Surgery and Traumatology of the Clinical Center of Vojvodina after the approval of the Ethics Committee. The retrospective study included 510 patients with ACL injury who underwent surgical treatment in the period from March 2013 to December 2015.

There were significantly more male patients (413, 81%) than female (97, 19%). The average age of patients was 27 years (15 to 59 years) with a standard deviation (SD) of 7.84.

The injury occurred during sports activity in 487 patients (95%), 13 patients had a fall injury (3%), and 10 (2%) were involved in a traffic accident. There were 282 persons in recreational sports (55%), 205 respondents were professional athletes (40%), while 23 respondents were not active in sports (5%). Among the athletes, 58 (11.4%) were competitors at international level, 105 (20.6%) at national, 101 (19.8%) at regional, and 225 (44.1%) at local level.

A total of 272 soccer players underwent surgery, as well as 46 handball players, 39 basketball players, 27 skiers, 21 volleyball players, 20 wrestlers, 18 judokas, 17 karate players, 11 American football players, 10 taekwondo competitors, 4 tennis players, 1 active in athletics and 1 in table tennis. Thus, most of our patients were soccer players (55.9%), since all other sports accounted for less than 10% of the total sample.

The right knee was operated in 281 cases (55.1%), the left in 212 (41.6%), while injuries of both knees were registered in 17 persons (3.3%).

Patients who signed a written consent to participate in the study were sent a Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire by e-mail [21], to which they responded voluntarily at least one year after surgery. In addition to data on the postoperative quality of life, general data were collected about the etiology of injuries in terms of professional and recreational sports, daily activities and possible knee instability. Data on each patient included the following parameters: gender and age, mode of injury, type and level of sports activity, laterality, associated injuries, time elapsed from injury to diagnosis, from injury to surgery, and postoperative values of all segments of KOOS questionnaire including symptoms, pain, daily activities, issues related to sports and quality of life, as well as the Tegner Lysholm Knee Scoring Scale. The KOOS questionnaire is a 42-item self-administered questionnaire with five subscales. Each question has 5 possible answers (Likert boxes). The score is a percentage score from 0 to 100, with 0 representing extreme problems and 100 representing no problems.

Anthropometric data of body weight and body height **(Table 1)** were collected and based on them the BMI was determined [19]. The BMI is calculated by dividing a person's weight by the square of their height (kg/m^2 – BM/BH^2). After the BMI was determined, patients were classified into 5 categories. Malnutrition is a BMI < 18.5, normal or healthy weight range is between 18.5 and 24.9, overweight is 25 – 29.9, mild obesity 30 – 34.9, and severe obesity is above 35 **(Table 2)**.

The descriptive statistics included the following: mean, SD, minimum and maximum. We performed one-way analysis of variance (ANOVA) and F-test. The T-test for independent samples was used in comparative statistics. The results were analyzed and presented in tables. The respondents who did not fill out the KOOS questionnaire voluntarily or completely, as well as those who did not complete the rehabilitation, were excluded from the study.

Results

The average body weight of in our patients was 80.64 kg (SD 8.07). A female patient had the lowest body weight of 52 kg, and a male patient had the highest body weight of 125 kg **(Table 1)**. The average body height was 1.80 m, minimum 1.56 m, maximum 2.05 m (SD = .08) **(Table 1)**.

Most of the patients included in the study had a normal body weight (302, 59%); there were 179 who were overweight (35%), 24 were mildly obese (5%), 5

Table 1. Body height and body weight
Tabela 1. *Telesna visina i masa*

	Minimum/*Minimum*	Maximum/*Maksimum*	Mean/*Prosek*	Standard deviation/*Standardna devijacija*
Weight/*Težina*	52	125	80.64	8.07
Height/*Visina*	1.56	2.05	1.80	.08

Table 2. Distribution of BMI categories of patients
Tabela 2. *Grupe pacijenata prema indeksu telesne mase*

Category *Kategorija*	BMI (kg/m^2) *Indeks tel. mase* (kg/m^2)	No. patients *Br. pacijenata*	Percentage *Procenti*
Underweight/*Pothranjeni*	< 18.5	5	1%
Healthy weight/*Fiziološki uhranjeni*	18.5 - 24.9	302	59%
Overweight/*Predgojazni*	25 – 29.9	179	35%
Obesity/*Gojazni*	30 – 34.9	24	5%
Severe obesity/*Teško gojazni*	≥ 35	0	0%
Average/*Prosek*	24.65	510	100%

Table 3. Correlation between knee instability and BMI
Tabela 3. *Korelacija nestabilnosti kolena sa vrednošću indeksa telesne mase*

Knee instability *Nestabilnost kolena*	No./*Br*	BMI/*(prosek)*	SD/*St. dev.*	Minimum/*Minimum*	Maximum/*Maksimum*
Never/*Nikada*	345	24.40	2.89	16.52	34.77
Rarely/*Retko*	119	25.38	3.22	18.99	34.63
Sometimes/*Ponekad*	39	24.82	3.26	19.41	33.14
Mostly/*Uglavnom*	6	23.28	2.52	20.05	25.95
Always/*Uvek*	1	23.83		23.83	23.83
Total/*Ukupno*	510	24.65	3.01	16.52	34.77

(1%) were malnourished, while there were no severely and extremely obese persons. The lowest BMI was 16.52, the highest 34.77, and the mean 24.65 (SD 3.01) **(Table 3)**.

A statistically significant difference was found between BMI and gender of the participants, T (508) = 9.35, p = .00 (p < .01), because on average, men had higher BMI (25.21) than women (22.26).

There was a statistically significant correlation between the age of subjects and BMI. The difference was moderately high: r = .442, p .000 (p < .01). Thus, BMI increases with age.

A statistically significant relationship was found between age and BMI groups (malnourished, normally fed, overweight or slightly obese patients): F (3,507) = 27,763, p = .000, p < .001).

The mean BMI among patients who sustained a sports injury was within the normal range (18.5 - 24.9), while persons who suffered an ACL injury in a traffic accident or had a fall injury had an increased mean BMI (> 25). Thus, there is a statistically significant difference between the BMI and how the injury was sustained (F (2.508) = 9.958, p = .000, p < .001).

On average, athletes have an ideal BMI (18.5 - 24.9), while recreational athletes and non-athletes have an increased mean BMI (BMI > 25), showing a statistically significant difference: F (2.508) = 29.334, p = .00, p < .001.

A statistically significant difference was observed between the BMI and the level of sports activity among the respondents: F (4.506) = 19.12, p = .000, p < .001. Athletes competing at the international, national and regional levels had ideal BMI, whereas recreational athletes and non-athletes had increased mean BMI (> 25).

We also found a significant correlation between BMI and Tegner score: r = -.282, p = .000 (p < .01) The results indicate that higher BMI is associated with lower Tegner score, which means that obese people are less engaged in professional sports with the highest risk of ACL injury. Therefore, we did not have a single obese soccer player at the national and international level of competition in the sample (with Tegner score of 10).

The BMI showed no statistically significant correlation with the "pain" subscale of the KOOS questionnaire. The correlation of BMI with "activities of daily living" showed the following results: r = .126, p = .000 (p < .01), which indicates that subjects with higher BMI are less active in daily activities. The difference is not high, but it is significant.

The BMI also showed a statistically significant correlation with "sports and recreational activities":

r = .133, p = .000 (p < .01), meaning that people with higher BMI are less active in sports and recreational activities.

The correlation of BMI and the KOOS subscale "subjective symptoms" showed a statistically significant difference only for the question: "How often do you feel knee instability?" The differences were found among those who answered: "rarely" and "mostly". The one-way ANOVA showed a significant difference: F (4,505) = 2.715, p = .029 (p < .05) **(Table 3)**.

Analyzing the quality of life after ACL reconstruction, we found that most patients (91.0%) felt that their general health was much better than before surgery showing that this surgery significantly improves the quality of life **(Table 3)**.

Comparing the BMI and the patients' personal perception of the impact of the injury on their quality of life, 345 (67.6%) of those with an ideal BMI responded that the surgery did not negatively affect their quality of life at all **(Table 3)**.

Patients with ideal BMI have a better perception of their own health compared to patients with higher or lower BMI. Respondents are often aware of their knee problem, but no significant association was found between the BMI and their awareness of the knee problem.

The correlation of BMI and overall quality of life with the "KOOS" questionnaire showed a low but significant correlation: p = .003 (p < .01) which indicates that the increase in BMI decreases the quality of life.

All three groups of patients who reported having knee instability of the operated knee: "sometimes", "often" or "always", had physiological BMI levels **(Table 3)**. During the 2 – 5 year period after the primary surgery, 18 patients (3.5%) underwent revision ACL surgery. Their mean BMI was 24.80, showing that postoperative ruptures most often occur in normal weight athletes.

Discussion

Fifty years ago, complete ACL rupture was the most common reason for the termination of a sports career [10, 16]. Today, with the development of surgical techniques, about two thirds of athletes successfully return to unrestricted sports activities 6 – 9 months after the ACL reconstruction [10, 12, 14, 16, 20]. Of the total number, 67.6% of our patients with ideal BMI also believe that a year after the surgery their quality of life has not changed at all. Therefore, sports medicine and traumatology is focused on finding risk factors for injuries and the development of training processes to avoid them [3, 4, 16].

Depending on the type of sport and due to anatomical and hormonal reasons, women are at 2 – 6 times higher risk of ACL injury [1, 24–26], but there are few studies in Serbia in which the female sex dominates, which is also the case in our study (81% of respondents are men). Although women are at a higher risk of ACL injury due to lesser muscle strength, increased knee valgus, wider pelvis, hormones that affect ligamentous hyperelasticity, narrower intercondylar femoral notch and other factors [1–4, 16], surgeries are more common in the male population [5–14, 23]. The analysis of ACL reconstructions in America shows that 61% of high school students who train basketball are girls, and only 39% are boys [4]. However, after high school, in the same group males were almost 7 times more likely to be injured. The comparison of sex distribution among the athletes of the same first league shows that female basketball players are at a 3.5 times higher risk of ACL injury than male basketball players, and female soccer players are at a 2.67 times higher risk than male soccer players [26]. In our earlier study, we concluded that the overall quality of life after ACL reconstruction did not differ significantly between males and females [7].

In our study, the majority of examinees were athletes, aged between 18 and 25 years, because injuries commonly occur at that age [5–10, 23, 27]. The ACL ruptures are most often caused by non-contact mechanisms, during a sudden change in direction and single-legged landing, at the end of the competition, due to muscle fatigue and lack of concentration [5, 24, 25, 28]. It has been established that neuromuscular body control, especially of the hips and lower extremities, adequate strength and proprioception contribute to the prevention of knee injuries [3, 16]. Muscle fatigue is a significant risk factor for ACL injury, due to weaker neuromuscular stabilization and risky movements of the knee joint [24, 28].

High risk activities for ACL injury include contact sports with rapid changes in direction and landings: soccer [3, 5], basketball [25, 29], handball [22] and American football [30]. Skiing is a non-contact sport with the highest risk of knee injury [31]. The most popular sport in the world is soccer with an estimated 265 million active players [3], so in our study, recreational soccer players were the most often injured. The incidence of ACL injuries also depends on the popularity of a certain sport in different countries, so most studies in Serbia are dominated by soccer players [5–7, 9, 10, 14, 17, 20], in the Nordic countries by handball players and skiers [20, 32], in the USA by rugby and basketball players [4, 30], in Japan by female basketball players, wrestlers and skiers [31, 33]. Due to the absence of shoe-surface friction, ACL injuries are extremely rare among hockey players, skaters and ballet dancers [5–7]. In our previous studies, including about 4.000 operated patients, we did not have a single case of surgical treatment in professional ice hockey players, ballet dancers and dancers [5–10], so we mistakenly thought that injuries do not occur among them. However, in the American Hockey League, there are 6 – 7 hockey players with ACL injury in every season [34], because this sport also requires sudden changes in direction, rotation of the knee joint and pivoting. Although the incidence of ACL injuries among hockey players is significantly lower than in other contact sports, tangling skates and falling to someone's knee can lead to rupture. Despite successful surgeries, American hockey players show that injuries have consequences, since the operated players

have lower success in terms of achieving a lower average number of goals per match and season [34].

The largest published series of ACL ruptures among ballet dancers included 12 injuries during a five-year follow-up in New York [24]. Each ballet dancer performs over 200 jumps during a 1.5-hour workout per day, more than half of which involve landing on one leg [24], which is particularly risky for ACL injury. However, only 0.2% of ballet dancers and 0.4% of contemporary dance competitors experience ACL injury [24], while among team ball sports 1 – 8% of competitors suffer ACL injury [25, 29, 35]. The reason for a low incidence of ACL injuries among dancers lies in the fact that their professional activity requires special skills in balance movement and landing control. Unlike most sports, ballet is more focused on the technique of performing risky knee movements, whereas athletes are focused on scoring goals and points, as well as contact with opposing players [24]. Also, professional ballet dancers and contemporary dancers usually have ideal body weight, because those with ACL injury have a mean BMI of 26.5 and those without injury 25.5 [24]. The reason for rare ACL injuries in ballet dancers lies in the fact that their movements are routine, practiced daily, with elegant arm movements that contribute to balance, without improvisation and influence of the environment, field and opposing players [24]. So, although ballet dancers do not belong to obese people, they also experience ACL ruptures. Obesity is a major epidemiological problem, both in the world and in our country. Over the last 40 years, the mean BMI in the female population of Serbia has increased from 24.1 to 25.3 [36]. In males, obesity has increased even more, from 23.8, to a mean BMI of 26.3 [36]. Today, more than half (54%) of the adult population of Serbia is overweight and 37% are obese [36]. The mean BMI in the general population of Serbia is about 26 [36], and in our sample 24.6, because it is dominated by athletes. The mean BMI in other studies that followed athletes ranged between 23.3 and 27.6 [24, 27, 37, 38]. Our study shows that there is a statistically significant difference between BMI and gender of respondents, since males have a higher BMI (average 25.21) than females (22.26), which is consistent with other studies [26, 27, 37].

According to the literature, BMI is a risk factor for ACL injury, especially in young athletes [39 - 41]. Women with increased body weight are at more than three times the risk of ACL injury than women with a normal BMI [40, 41]. Body height, especially during growth of the tibia and femur at puberty, leads to a shift in the center of gravity, which complicates neuromuscular control [16]. The increase in body weight directly affects the increase of forces acting on the knee joint during sports movements of strong intensity [16]. The most hazardous positions for ACL injury are flexion, abduction, valgus, anterior translation, and external tibial rotation [4, 42, 43]. Athletes, like in our study, have statistically significantly lower BMI compared to non-athletes [44]. The analysis of 140 athletes of both sexes from Novi Sad training volleyball, basketball, soccer, handball, athletics and rowing, showed that BMI in all groups ranged in physiological limits, except in the group of male handball players, whose mean BMI was moderately higher (25.70) [45]. The average values of body fat percentage were significantly lower among female athletes, with the lowest values in women's athletics, while, among men, basketball players had the highest percentage of fat [45].

Modern questionnaires prove the importance of the patient's perception in assessing their own health [5, 7, 8], so we found that an increase in BMI reduces the quality of life in patients undergoing ACL reconstruction. Obese patients (BMI > 25) show a lower postoperative quality of life compared to normal weight patients. The difference is not high, but it is statistically significant. Kowalchuk et al. [46], like us, found that patients with BMI > 30 had less successful ACL reconstruction results than patients with physiological BMI. Other studies confirm that BMI can change the quality of life of patients after ACL reconstruction [47, 48]. It has also been shown that patients with BMI over 35 have poorer postoperative results after arthroscopic meniscectomy than patients with BMI < 30, because postoperative "KOOS" results are better in normal weight patients than in obese individuals [49, 50]. In an earlier study, we found that increased BMI was also associated with higher incidence of ACL injury associated with meniscus injuries [51].

In adults, increased BMI is often associated with knee osteoarthritis [27], which explains why obese people with elevated BMI have a lower level of postoperative activity after ACL revision. Ankle injuries are about 19 times more common among athletes with increased BMI and a previous ankle sprain, compared to athletes with a previous ankle sprain and with normal BMI [52]. Considering that after surgery most patients spend most of their time inactive, there may be an imbalance between energy intake and expenditure. Therefore, after some time, they gain weight and even though they are athletes, they have an increased BMI [27]. The postoperative quality of life is also affected by subsequent ACL injuries, because within 2 – 3 years after unilateral injury, about 3% of patients experience contralateral rupture [53, 54]. Also, ACL injuries may cause chronic knee instability, muscle weakness, and early onset of osteoarthritis [54, 55]. Professional sports and biomechanical joint stress are the main reasons for the pathogenesis and progression of knee osteoarthrosis [56]. Losing 1 kg of body weight results with a 4-fold reduction in the load exerted on the knee per step during daily activities [56]. A loss of 5% of the total body weight in obese adults with knee osteoarthritis over 18 months results in an 18% improvement in the knee function and if combined with exercise, the mobility improves by 24% [56].

Some studies have concluded that increased BMI may also be a potential risk factor for revision surgery after primary ACL reconstruction [18, 30]. American rugby players also have a significantly increased risk for new injuries if they are overweight and had a former ACL injury [30]. In contrast, other authors believe that

there is still insufficient evidence that BMI is a significant risk factor for ACL rerupture [38, 47, 57], since the mean BMI of patients with primary rupture is 27.6, and it is slightly higher among revision surgeries (27.8) [38]. Our study showed similar findings (24.65 in primary vs. 24.80 in revision). The above studies, like ours, found that factors such as gender, body weight, height, and BMI were not significant factors for reinjury and revision ACL reconstruction [38, 47, 57], and the causes should be sought in incorrect position of bone tunnels, new traumas, and premature return to sports activities [7, 9, 10, 58, 59].

The disadvantage of this study is the subjectivity of the respondents. The study raises dilemmas related to surgical treatment of obese patients (whether they should undergo surgery or lose weight first). There is no consensus on whether to define a marginal BMI for safe ACL reconstruction, which may be the basis for future research. Since we did not have extremely obese respondents in the sample, our study imposes a potential hypothesis of future studies: are excellent results of ACL reconstructions partly due to the fact that obese people get injuries less often because they do not play sports, or obese persons with injuries do not want surgery. Perhaps orthopedic surgeons adhere to strict selection of patients for reconstruction, so that being overweight would not lead to bad results.

A recent large-scale study [57] showed that fear of surgical procedures in obese patients is irrational; it compared the outcomes of primary ACL reconstructions between the normal weight and overweight patients (BMI > 25) and found that in obese patients the risk for arthritis was significantly higher, but the risk for revision surgery or contralateral ACL tear was lower [57]. There was no significant difference in complication rates and in the majority of functional scores [57]. In addition, if we knew all the causes of injuries, we would know how to prevent them and treat them more successfully.

Conclusion

By determining the body mass index, it was established that the highest prevalence of patients undergoing anterior cruciate ligament reconstruction were normal weight patients (athletes). Men have a higher mean body mass index than women and older athletes have an increased mean body mass index. Individuals injured in traffic accidents and in daily activities have a higher mean body mass index than those injured in sports. Professional athletes have a body mass index within ideal limits, while recreational and non-athletes have elevated mean values. The association between the body mass index and the level of sports activity is significant. The body mass index is not a significant factor for reinjury and revision reconstruction. The anterior cruciate ligament reconstruction contributes to better quality of life since the majority of patients (91.0%) rated their general health as much better than before surgery, and 67.6% of patients with ideal body mass index thought that surgery did not affect their quality of life at all. Increased body mass index (> 25) is associated with lower quality of life after surgery.

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CONE-BEAM COMPUTED TOMOGRAPHY ASSESSMENT OF THE BUCCAL BONE THICKNESS IN ANTERIOR MAXILLARY AND MANDIBULAR TEETH

PROCENA DEBLJINE BUKALNE LAMELE MAKSILE I MANDIBULE U PREDELU PREDNJIH ZUBA POMOĆU KOMPJUTERIZOVANE TOMOGRAFIJE KONUSNOG SNOPA

Saša MARIN[1], Aleksandra ĐERI[2], Helena VIDOVIĆ[1], Nataša TRTIĆ[3], Adriana ARBUTINA[4] and Verica PAVLIĆ[3]

Summary

Introduction. The aim of this study was to assess the buccal bone thickness in anterior maxillary and mandibular teeth and to provide information important during immediate implant placement. **Material and Methods**. The study included 245 cone-beam computed tomography scans. The buccal bone thickness was measured in the sagittal plane of the maxillary and mandibular anterior teeth at five points (M1 - M5) (2 mm apart), starting 2 mm from the cementoenamel junction in the coronal to apical position along the roots. **Results**. The lowest mean buccal bone thickness was observed at M1 point in all teeth in both jaws while the highest mean buccal bone thickness was observed at M4 (maxilla) and M5 (mandible). An increase of the buccal bone thickness was established at every subsequent measurement point perpendicular to the long axis of the tooth ($p < 0.001$). The buccal bone thickness was less than 1 mm in more than 60% of all teeth in the maxilla and mandible at all measurement points. A statistically significant difference in the thickness of the buccal bone in relation to the patients' age was found at all measurement points, except at M4 point of the anterior teeth of the maxilla ($p = 0.456$) and mandible ($p = 0.109$). **Conclusion**. The buccal bone thickness in anterior maxillary and mandibular teeth is less than 1 mm in more than 60% at all measurement points. The buccal bone thickness tends to increase from a coronal to apical position along the roots.

Key words: Cone-Beam Computed Tomography; Alveolar Process; Incisor; Esthetics, Dental; Immediate Dental Implant Loading; Alveolar Bone Loss; Bone Resorption; Gingival Recession

Sažetak

Uvod. Cilj istraživanja je bio izmeriti debljinu bukalne lamele u predelu prednjih zuba gornje i donje vilice i obezbediti informacije koje su značajne prilikom imedijatne ugradnje implantata. **Materijal i metode.** U istraživanju je analizirano 245 snimaka urađenih pomoću konusnog snopa kompjuterizovane tomografije. Merenje debljine bukalne lamele je obavljeno na sagitalnom preseku maksilarnih i mandibularnih prednjih zuba na pet tačaka (M1-M5) (udaljenih 2 mm jedna od druge), počevši 2 mm od cementno-gleđne granice u koronarno-apikalnom pravcu duž korena zuba. **Rezultati.** Najniža srednja vrednost debljine bukalne lamele uočena je na M1 mernoj tački na svim zubima u obe vilice, dok su najveće srednje vrednosti bile na M4 (maksila) i M5 (mandibula). Sa svakom sledećom tačkom merenja uzdužno uz osu zuba dolazi do povećanja vrednosti debljine bukalne lamele ($p < 0,001$). Debljina bukalne lamele je manja od 1 mm u više od 60% tačaka merenja, na svim prednjim zubima maksile i mandibule. Statistički značajna razlika debljine bukalne lamele u odnosu na starost pacijenta je bila na svim mernim tačkama osim na tački M4 prednjih zuba maksile ($p = 0,456$) i mandibule ($p = 0,109$). **Zaključak.** Maksilarni i mandibularni prednji zubi imaju debljinu bukalne lamele manju od 1 mm u više od 60% svih tačaka merenja. Debljina bukalne lamele ima tendenciju povećanja debljine u koronarno-apikalnom pravcu duž korena zuba.

Ključne reči: kompjuterizovana tomografija sa konusnim snopom; alveolarni nastavak; sekutić; dentalna estetika; imedijantno opterećenje implantata; gubitak alveolarne kosti; resorpcija kosti; povlačenje desni

Introduction

Immediate implant placement, defined as the placement of dental implant immediately into fresh extraction socket site after tooth extraction, has advantages over early and delayed placement. In addition to the reduction of treatment time, number of interventions, and patient discomfort, the main advantages include soft and hard tissues conservation after tooth extraction [1, 2]. Furthermore, there is no difference in the survival rates between implants placed with immediate placement protocol and other protocols [3].

However, lack of success in achieving desirable esthetic outcomes due to recession of buccal mucosa is still one of the most common complications when it comes to immediate implant placement. Adequate

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Abbreviations

BBT – buccal bone thickness
CBCT – cone-beam computed tomography
CEJ – cementoenamel junction

buccal bone and soft tissue thickness are essential for long-term esthetic outcomes [4].

Soft tissue thickness has been shown to be dependent on the thickness of the underlying bone. The presence of minimum buccal bone thickness (BBT) of 2 mm is critical for the maintenance of the vertical dimension of the alveolar crest after tooth extraction and soft tissue stability [5–7]. Also, thin buccal bone may cause a local risk associated with significantly greater vertical bone resorption over time and subsequent gingival recession [8].

The bone resorption is rapid in the three-month period compared to the following nine months [9]. Both buccal and palatal bone plates show bone loss after tooth extraction. The buccal bone plate is more affected since the resorption is more severe where the walls are initially thinner and composed mainly of bundle bone. There is more reduction in the width than in the height of the residual alveolar ridge after tooth extraction [10, 11].

Various techniques have been proposed to overcome the limitations of a thin buccal bone. The bone resorption may be reduced by using bone graft barrier membranes when the BBT is less than 2 mm [12]. The socket shield technique has positive effects on the changes in width and height of buccal bone plate and may be a good alternative in terms of alveolar bone maintenance [13, 14].

Despite immediate implant placement, the remodeling of the alveolar bone is an inevitable process. However, the resorption degree is in correlation with initial BBT and, therefore, the treatment outcomes [15, 16].

Considering the significance of the buccal cortical bone thickness as one of the risk factors for esthetic outcome after immediate implant placement, it is of great importance to perform a precise bone assessment prior to performing any surgical procedure. Cone beam computed tomography (CBCT) offers high-resolution and cross-sectional imaging. This is an imaging technique that enables accurate bone structure measurements and comprehensive preoperative implant site assessment. Nowadays, CBCT has become a method of choice in dental implant treatment planning [17, 18].

In this study, CBCT images were used to evaluate the BBT in the anterior maxillary and mandibular teeth. The objective was to find the correlation between the BBT in regard to patients' age and gender. The study aimed to provide more quantitative information about maxillary and mandibular anterior area thickness in order to help immediate implantation planning.

Material and Methods

After the study was approved by the Scientific Ethics Committee of the Faculty of Medicine, University of Banja Luka (18/4.6/20), CBCT scans were collected and analyzed using the Planmeca ProMax 3D Classic (Planmeca, Finland) with a voxel size (VS) of 0.2 mm and maximum field of view (FOV) 110 × 80 mm. The study was designed as a retrospective study to evaluate BBT of the anterior maxillary and mandibular teeth. The CBCT scans were done for various clinical reasons between January 2018 and December 2018.

The inclusion criteria for the study were: high-resolution images, presence of maxillary and mandibular anterior teeth (left canine to right canine), no severe periodontal bone loss, and no periapical diseases.

The exclusion criteria were: scans with poor image definition, presence of severe periodontal bone loss, periapical diseases, previous apical surgery, root resorption. Supernumerary, misaligned and crowded teeth in the anterior region were excluded, since accurate measurements could not be obtained.

The measurement of BBT was conducted in the buccal-oral direction of the maxilla: right side - central incisor (11), lateral incisor (12), canine (13) and left side: central incisor (21), lateral incisor (22), canine (23); and mandibula: left side - central incisor (31), lateral incisor (32), canine (33) and right side - central incisor (41), lateral incisor (42), canine (43).

For each tooth, measurements were taken at five points (M1 - M5), starting 2 mm from the cementoenamel junction (CEJ). Every subsequent measurement point was recorded with a 2 mm distance from the previous measurement point perpendicular to the long axis of the tooth **(Figures 1** and **2)**. The measurement of the BBT was performed in the sagittal plane.

All CBCT images were analyzed by two trained observers. If differences in measurements were found, an average of two measurements was calculated.

The statistical analysis was performed using Statistical Package for the Social Sciences (IBM SPSS statistics 25.0, IBM Corporation, New York, United States) at a 5% significance level. The data were presented with descriptive statistics. The normality of distribution was assessed using Shapiro-Wilks test. Kruskal Wallis and Mann-Whitney tests were used for quantitative and continuous variables.

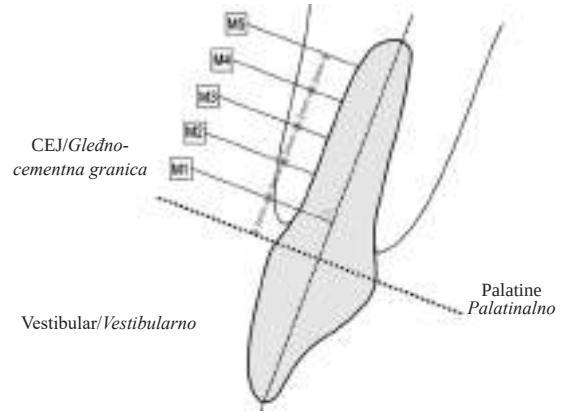

Figure 1. Representation of BBT measurements of the anterior maxillary teeth. Measurements were done at five points (M1 – M5), starting 2 mm from CEJ
Slika 1. *Prikaz merenja debljine bukalne lamele maksilarnih prednjih zuba. Merenja su beležena na pet tačaka (M1 – M5), počevši 2 mm od cementno-gleđne granice*

Results

A total of 245 CBCT scans were included in this study, 131 (53.47%) males and 114 (46.53%) females. The mean age of all patients was 45.5 years (mean age for males 47.00 ± 13.68; mean age for females 45.00 ± 14.42).

Table 1 and **Table 2** present descriptive statistics for BBT per tooth at M1, M2, M3, M4 and M5. The lowest mean BBT was observed at the M1 measurement point in all teeth in both jaws (maxilla and mandible). There was an increase in BBT perpendicular to the long axis of the tooth with every subsequent measurement point ($p < 0.001$). The highest mean BBT was at M4 (maxilla) and M5 (mandible) measurement points **(Table 1)**.

Table 2 shows that BBT was thinner than 1 mm in more than 60% of all teeth in the maxilla and mandible at all measurement points. Furthermore, BBT was thinner than 1 mm in more than 90% at measurement points M1 and M2. In the maxilla, the incidence of BBT thicker than 1 mm was more than 25% only at the M3 measurement point. This incidence was even lower in the mandible. The incidence of BBT thicker than 2 mm was very rare, and it was found mostly at the M5 measurement point **(Table 2)**.

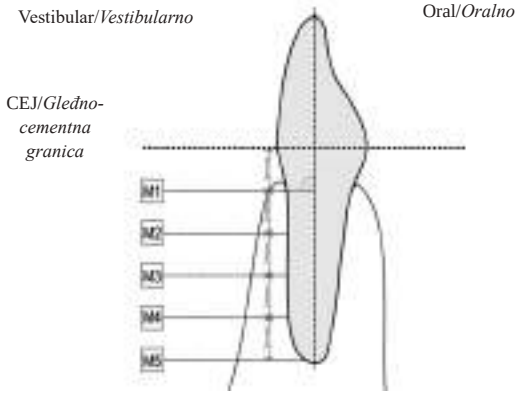

Figure 2. Representation of BBT measurements of the anterior mandibular teeth. Measurements were done at five points (M1 – M5), starting 2 mm from CEJ
Slika 2. *Prikaz merenja debljine bukalne lamele mandibularnih prednjih zuba. Merenja su beležena na pet tačaka (M1-M5), počevši 2 mm od cementno-gleđne granice*

Table 1. BBT of maxillary and mandibular anteriror teeth at each point of measurement
Tabela 1. *Debljina bukalne lamele maksilarnih i mandibularnih prednjih zuba na svim tačkama merenja*

Tooth *Zub*	M1			M2			M3			M4			M5			p/*p*
	Mean/ *Srednja* ± SD	Min *Minimun*	Max *Maksimum*	Mean/ *Srednja* ± SD	Min *Minimun*	Max *Maksimum*	Mean/ *Srednja* ± SD	Min *Minimun*	Max *Maksimum*	Mean/ *Srednja* ± SD	Min *Minimun*	Max *Maksimum*	Mean/ *Srednja* ± SD	Min *Minimun*	Max *Maksimum*	
11	0.034 ± 0.172	0.000	1.170	0.219 ± 0.421	0.000	1.520	0.758 ± 0.504	0.000	1.810	0.915 ± 0.375	0.000	2.040	0.911 ± 0.384	0.000	2.510	<**0.001**
12	0.024 ± 0.168	0.000	1.610	0.191 ± 0.431	0.000	2.210	0.731 ± 0.597	0.000	2.610	0.885 ± 0.475	0.000	2.210	0.861 ± 0.385	0.000	2.200	<**0.001**
13	0.016 ± 0.113	0.000	0.800	0.168 ± 0.450	0.000	3.620	0.671 ± 0.661	0.000	4.420	0.892 ± 0.535	0.000	3.690	0.818 ± 0.440	0.000	2.600	<**0.001**

Legenda: SD – standardna devijacija
*Shows significantly higher proportion at 5% level of significance/**Pokazuje značajno veće vrednosti na nivou značajnosti od 5%*

Table 2. Distribution of BBT (%) for maxillary and mandibular anterior teeth
Tabela 2. *Raspodela debljine bukalne lamele u procentima za maksilarne i mandibularne prednje zube*

Tooth *Zub*	< 1 mm					1 – 2 mm					> 2 mm				
	M1 (%)	M2 (%)	M3 (%)	M4 (%)	M5 (%)	M1 (%)	M2 (%)	M3 (%)	M4 (%)	M5 (%)	M1 (%)	M2 (%)	M3 (%)	M4 (%)	M5 (%)
11	99.35	91.03	65.20	60.30	64.10	0.65	8.97	37.8	39.1	34.62	0.00	0.00	0.00	0.64	1.28
12	99.26	94.07	64.44	62.22	73.33	0.74	5.19	34.82	36.3	25.19	0.00	0.74	0.74	1.48	1.48
13	100.00	95.94	68.92	59.46	68.92	0.00	3.38	27.03	37.84	29.73	0.00	0.68	4.05	2.7	1.35
21	100.00	92.76	69.08	65.79	67.11	0.00	7.24	28.95	34.21	30.92	0.00	0.00	1.97	0.00	1.97
22	100.00	94.80	65.19	61.48	73.89	0.00	5.20	34.07	34.07	22.39	0.00	0.00	0.74	4.44	3.73
23	100.00	95.27	70.95	70.27	72.00	0.00	4.73	27.03	26.35	26.00	0.00	0.00	2.03	3.38	2.00
31	99.08	95.41	89.91	88.07	70.64	0.92	4.59	9.17	10.09	27.52	0.00	0.00	0.92	1.84	1.84
32	99.12	95.57	87.61	86.73	82.15	0.88	4.43	12.39	13.27	16.96	0.00	0.00	0.00	0.00	0.89
33	100.00	94.02	89.74	88.89	91.45	0.00	5.98	8.55	10.26	7.69	0.00	0.00	1.71	0.86	0.86
41	100.00	96.23	83.02	88.07	70.64	0.00	3.77	15.09	10.09	27.52	0.00	0.00	1.89	1.84	1.84
42	100.00	98.26	87.83	84.35	83.48	0.00	1.74	12.17	15.65	16.52	0.00	0.00	0.00	0.00	0.00
43	98.26	94.78	83.48	91.30	85.09	1.74	5.22	16.52	8.70	14.91	0.00	0.00	0.00	0.00	0.00

Table 3. Relationship between patients' age and mean BBT at each point of measurement
Tabela 3. *Odnos između godina pacijenata i prosečnih srednjih vrednosti debljine bukalne lamele na svim tačkama merenja*

Age/*Godine*	<18	18–30	30–50	50–70	>70	p/*p*
Maxilla *Gornja vilica*	Mean *Srednja* ± SD	Mean *Srednja* ± SD	Mean *Srednja* ± SD	Mean *Srednja* ± SD	Mean *Srednja* ± SD	
M1	0.122 ± 0.301	0.017 ± 0.116	0.015 ± 0.123	0.009 ± 0.090	0.000 ± 0.000	**<0.001**
M2	0.655 ± 0.489	0.398 ± 0.464	0.179 ± 0.434	0.095 ± 0.286	0.000 ± 0.000	**<0.001**
M3	0.911 ± 0.327	0.881 ± 0.433	0.890 ± 0.736	0.591 ± 0.558	0.435 ± 0.555	**<0.001**
M4	0.908 ± 0.351	0.895 ± 0.341	0.948 ± 0.533	0.863 ± 0.458	0.778 ± 0.594	0.456
M5	1.042 ± 0.528	0.840 ± 0.321	0.901 ± 0.449	0.848 ± 0.415	0.745 ± 0.507	**0.001**
Manidible/*Donja vilica*						
M1	0.067 ± 0.231	0.081 ± 0.293	0.020 ± 0.137	0.004 ± 0.059	0.000 ± 0.000	**0.004**
M2	0.686 ± 0.322	0.461 ± 0.481	0.177 ± 0.356	0.102 ± 0.292	0.000 ± 0.000	**<0.001**
M3	0.733 ± 0.231	0.512 ± 0.459	0.565 ± 0.478	0.454 ± 0.517	0.144 ± 0.320	**0.007**
M4	0.752 ± 0.244	0.625 ± 0.629	0.731 ± 0.358	0.613 ± 0.434	0.485 ± 0.478	0.109
M5	1.028 ± 0.310	0.866 ± 0.656	0.794 ± 0.412	0.725 ± 0.379	0.848 ± 0.371	**0.001**

Legenda: SD – standardna devijacija
*Shows significantly higher proportion at 5% level of significance/**Pokazuje značajno veće vrednosti na nivou značajnosti od 5%*

Table 4. Relationship between patients' gender and mean BBT at each point of measurement
Tabela 4. *Odnos između pola pacijenata i prosečnih srednjih vrednosti debljine bukalne lamele na svim tačkama merenja*

Sex/*Pol*	Males/*Muškarci*	Females/*Žene*	
Maxilla/*Gornja vilica*	Mean/*Srednja* ± SD	Mean/*Srednja* ± SD	p/*p*
M1	0.009 ± 0.084	0.029 ± 0.165	0.036
M2	0.186 ± 0.390	0.204 ± 0.437	0.620
M3	0.740 ± 0.694	0.726 ± 0.562	0.972
M4	0.942 ± 0.505	0.864 ± 0.451	**0.001**
M5	0.924 ± 0.458	0.831 ± 0.398	**0.000**
Manidible/*Donja vilica*			
M1	0.017 ± 0.128	0.013 ± 0.112	0.697
M2	0.139 ± 0.332	0.184 ± 0.362	0.066
M3	0.512 ± 0.522	0.470 ± 0.462	0.214
M4	0.698 ± 0.428	0.597 ± 0.415	**0.001**
M5	0.785 ± 0.415	0.740 ± 0.410	**0.060**

Legenda: SD – standardna devijacija
*Shows significantly higher proportion at 5% level of significance/**Pokazuje značajno veće vrednosti na nivou značajnosti od 5%*

Kruskal-Wallis test was conducted to examine the differences in BBT in regard to age. This test showed that there were significant differences at every measurement point, except at M4 in both jaws (p = 0.456 maxilla, p = 0.109 mandible) **(Table 3)**.

A statistically significant difference among groups was assessed using the Man-Whitney U test for two independent variables: between males and females in maxilla at measuring points M1 (p = 0.036), M4 (p = 0.001), M5 (p = 0.000) and in mandible at measuring point M4 (p = 0.001) **(Table 4)**.

Discussion

This retrospective study evaluated BBT in the anterior maxillary and mandibular teeth using CBCT images over a one-year period. It also investigated the impact of age and gender on BBT.

Regarding the maxilla, the buccal bone was thinner at M1 than at M2 – M5 in all teeth. The highest mean BBT was found at M4, which is not in accordance with Gakonoyo et al. study [19], where the thickest measurement point was the furthest from the bone crest. This could be attributed to the different proximity of the measurement points. In our study, all measurement points were close to each other (2 mm apart), while in Gakonoyo et al. study, the first measurement point was 4 mm apical to the CEJ and the second was located in the middle of the root. According to the literature, the thinnest alveolar ridge is in the region of lateral central incisor compared to other anterior teeth regions of the maxilla. It is probably due to the presence of lateral fossa and concavity adjacent to lateral incisor [20].

In our study, the lowest BBT was mainly in the region of canines, with the exception of the region of teeth 21 at M1 (0.012 ± 0.102), 22 at M1 (0.006 ± 0.073), 12 at M4 (0.885 ± 0.475) and 21 at M4 (0.880 ± 0.357) and at M5 (0.867 ± 0.374) **(Table 1)**. The reason is probably the anatomical upright position of the canine root in the maxilla.

In the mandible, the lowest BBT was at M1, and the highest at M5. The values of BBT among the groups of teeth are variable, although the canines have thinner BBT than the central and lateral incisors at measurement points M4 and M5. Tsai et al. [21] investigated the risks for labial bone perforation in the anterior mandibular region using a virtual immediate implant placement procedure. They found that the prevalence of labial bone perforation is significantly higher at the mandibular canine site than at the central and lateral incisor sites.

In our study, the measured BBT in both jaws was very thin. More than 60% of all measurement points showed BBT less than 1 mm. The BBT from 1 – 2 mm was found rarely (22.39 – 39.1% in the maxilla only at measurement points M3 – M5). This is in accordance with Gakonoyo et al. [19] study results, where BBT in the maxillary anterior teeth was predominantly thinner at measurement points near the bone crest. The incidence of BBT thicker than 2 mm was very low and mostly found at measurement point M5 (1.28 – 3.73%). This incidence is even lower in the mandible **(Table 2)**. Al Tarwneh et al. [22] reported that teeth with a bone thickness of more than 2 mm account for no more than 3% at their best. Lack of sufficient buccal bone in the anterior region of the maxilla may lead to recession of the marginal peri-implant mucosa and adversely effect the final esthetic outcome [23]. Connective tissue grafting has a beneficial effect on the peri-implant mucosa and esthetic outcome [24]. However, Zuiderveld et al. [25] found that the application of connective tissue in the esthetic zone of immediately placed implants may lead to BBT decrease after 1 year. This may be due to disrupted vascularization between the mucosa and periosteum during connective tissue grafting.

The relationship between the patient age and BBT is still unclear. Some studies found that the patient age was associated with the BBT [26, 27], while others have failed to find a correlation [28]. We found a statistically significant difference in average mean values at every measurement point, except M4 in the maxilla ($p = 0.456$) and M4 in the mandible ($p = 0.109$). The highest BBT was found in younger patients in both jaws compared to other groups. Our results are in correlation with the Santos et al. findings [26].

Comparing average BBT at all measurement points in men and women, we found that males had greater BBT the closer we got to the apical direction. The results showed that males had higher values at M3, M4 and M5 measurement points and females at M1 and M2. A statistically significant difference was found in the maxilla at M1 ($p = 0.036$), M4 ($p = 0.001$) and M5 ($p < 0.001$) and in the mandible only at M4 ($p = 0.001$). The literature indicates that males have a greater BBT [22]. Although there are no significant differences between the values, there is a trend of greater BBT in males [29, 30]. Additionally, Zhang et al. [20] compared the width of the alveolar ridge in males and females in the anterior maxillary teeth. The results showed a wider alveolar ridge in males at all measurements.

The limitations of this study should be mentioned. The complete comprehensive patient medical history was unavailable, and the effect of the medical status on the BBT was not determined since the CBCTs used in this study were taken as a diagnostic adjunct to dental medicine and oral surgery therapy. Further studies with larger sample sizes would be needed to validate our findings.

Conclusion

Based on our results, the buccal bone plate is generally thin in the maxillary and mandibular anterior area. The buccal bone thickness was lower than 1 mm in more than 60% of all measurement points in all teeth in the maxilla and mandible. In the maxilla, more than 90% of patients presented with bone plate thickness under 1 mm at measurement points M1 and M2. This is even lower in the mandible. These findings could affect successful implant treatment in the esthetic zone. Precise buccal bone thickness measurement is crucial in implant treatment planning, especially in the maxillary and mandibular anterior area.

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ACUTE KIDNEY INJURY IN CRITICALLY ILL PATIENTS IN THE INTENSIVE CARE UNITS

AKUTNO OŠTEĆENJE BUBREGA KOD KRITIČNO OBOLELIH PACIJENATA U JEDINICAMA INTENZIVNE NEGE

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Summary

Introduction. Acute kidney injury is a serious complication in critically ill patients in the intensive care units. The incidence varies from 20% to as high as 80%. Acute kidney injury is associated with expensive supportive therapy, high morbidity and poor outcomes. The aim of this study was to determine the incidence, causes, risk factors, treatment options and treatment outcomes of acute kidney injury in critically ill patients. **Material and Methods.** The study included 44 patients, with an average age of 67 ± 13.20 years. The data were collected during a three-month prospective study at the Department of Emergency Internal Medicine of the Clinical Center of Vojvodina, Novi Sad. Demographic data were collected from the medical records, as well as data on blood tests, comorbidities, use of nephrotoxic agents, and treatment of these patients. **Results.** Of the 44 patients who were included in the study, 20% developed acute kidney injury. De novo acute kidney injury was diagnosed in 51.22% and 48.78% of patients had acute-on-chronic renal failure. The most common type of acute kidney injury was pre-renal, 80.95%. Comorbidities were present in all patients, most often arterial hypertension, in 52.4% of patients. Complete recovery of kidney function was found in 42.86% of patients and the mortality was 28.57%. Conservative therapy was used in 90.48% of patients, while 9.52% of patients required renal replacement therapy. **Conclusion.** De novo acute kidney injury was found in approximately half of the critically ill patients in the intensive care unit, mainly older patients with comorbidities. The most common type of acute kidney injury was pre-renal. Older age and comorbidities were associated with poor outcomes and high mortality.

Key words: Acute Kidney Injury; Intensive Care Units; Critical Illness; Diagnosis; Comorbidity; Incidence; Treatment Outcome; Mortality; Risk Factors

Sažetak

Uvod. Akutno oštećenje bubrega je ozbiljna komplikacija kod kritično obolelih pacijenata koji se leče u jedinicama intenzivne nege. Incidencija varira od 20% pa do više od 80%. Akutno oštećenje bubrega zahteva skupu suportivnu terapiju, morbiditet je povećan, a povezano je i sa lošim ishodom lečenja ovih pacijenata. Cilj ovog rada bio je da se utvrde incidencija, uzroci, faktori rizika, lečenje i ishod lečenja kritično obolelih sa akutnim oštećenjem bubrega. **Materijal i metode.** Studija je obuhvatila 44 pacijenta, prosečne starosti 67 ± 13,20 godina. Podaci su prikupljani tokom tromesečnog prospektivnog istraživanja na Odeljenju urgentne interne medicine Kliničkog centra Vojvodine u Novom Sadu. Iz medicinske dokumentacije prikupljani su demografski podaci, kao i podaci o načinjenim analizama krvi, komorbiditetima, upotrebi nefrotoksičnih supstancija i lečenju ovih pacijenata. **Rezultati.** Od ukupno 44 pacijenata uključnih u studiju, akutno oštećenje bubrega nastalo je kod 20% pacijenata. Od tog broja 51,22% imalo je de novo akutno oštećenje bubrega, a kod 48,78% dijagnostikovana je akutizacija hronične bubrežne slabosti. Najčešći oblik bio je prerenalni, 80,95%. Kod svih pacijenata bili su prisutni komorbiditeti, najčešće arterijska hipertenzija, kod 52,4% ispitivanih. Potpuni oporavak bubrežne funkcije zabeležen je kod 42,86% pacijenata. Mortalitet je bio 28,57%. Kod 90,48% pacijenata primenjena je konzervativna terapija, dok je kod 9,52% pacijenata primenjena neka od metoda zamene bubrežne funkcije. **Zaključak.** De novo nastalo akutno oštećenje bubrega zabeleženo je kod oko polovine pacijenata u jedinici intenzivne nege, najčešće starijeg životnog doba sa prisutnim komorbiditetima. Najčešća etiologija bila je prerenalna. Starije životno doba i prisutni komorbiditeti su povezani sa lošim ishodom lečenja. Mortalitet ovih pacijenata bio je visok.

Ključne reči: akutna bubrežna insuficijencija; jedinice intenzivne nege; kritično oboleli; dijagnoza; komorbiditet; incidenca; ishod lečenja; mortalitet; faktori rizika

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Abbreviations

AKI – acute kidney injury
ICU – intensive care unit
RRT – renal replacement therapy

Introduction

Acute kidney injury (AKI) is a common and serious complication in critically ill patients in the intensive care unit (ICU). It is associated with increased risks of in-hospital mortality and long-term chronic kidney disease. Some patients had kidney injury before admission to the ICU and others developed AKI in the first 72 hours [1, 2]. The time of onset of kidney injury implicates the difference in causes and severity of the disease, resulting in different clinical manifestations and outcomes. The incidence of AKI in the ICU varies from 20% to as high as 80%. A rapid increase in aging population with multiple comorbidities contributes to high incidence [1–3].

Up to 2004, more than 30 different definitions of AKI were used and this was a significant problem for clinicians. Consequently, it was very difficult to compare results of different studies, because different definitions of AKI were used [4]. In 2004, the Acute Disease Quality Initiative (ADQI) Group proposed the Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) criteria to allow for AKI to be objectively and uniformly defined. The severity of AKI was graded by the risk, injury, failure, and loss of kidney function [5–7]. In 2012, the group Kidney Disease: Improving Global Outcomes (KDIGO) published a new definition of AKI to help clinicians to improve care and outcomes of patients with AKI [8].

Determination of the etiology and risk factors of AKI were the initial goals of our study. Furthermore, our aim was to determine the pre-renal (cardiorenal syndrome, including heart failure and venous congestion, hemorrhagic, hypovolemic and septic shock, abdominal compartment syndrome, kidney transplant, including delayed graft function, medication, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), intra-renal [thrombotic microangiopathies, cholesterol embolism, anti-glomerular basement membrane disease and immune complexes and anti-neutrophilic cytoplasmic autoantibody vasculitis, sickle cell anemia, systemic infections and sepsis, pyelonephritis, drug-related or heavy metal-related tubule necrosis, crystal-induced nephropathy, myoglobin (rhabdomyolysis), contrast media, light chains (monoclonal gammopathies) and metabolites (acute urate nephropathy and acute oxalate nephropathy), acute cellular rejection, acute interstitial nephritis, immune checkpoint inhibitor-related and cytokine release syndrome, T-cell therapy], and post-renal (urinary tract obstruction, bilateral ureteral obstruction, bladder dysfunction and urethral obstruction) causes of AKI [1, 9–11]. These data are very important for prevention of AKI as well as for treatment initiation, because some forms of AKI are reveresible if the treatment is started immediately after diagnosis. Risk factors for AKI include old age, chronic kidney disease, comorbidities such as diabetes mellitus, hypertension, and cardiovascular disease [1–3, 8, 10–12].

Treatment of AKI should begin by hemodynamic stabilization, identification of complications (hyperkalemia, metabolic acidosis, anemia, and fluid overload) and the cause of AKI [12–16]. If conservative treatment appears not to be effective enough, initiation of renal replacement therapy (RRT) should be considered [2, 3, 14, 16–18]. Indications for the initiation of RRT include anuria, severe/refractory hyperkalemia, severe/refractory metabolic acidosis, refractory volume overload, severe azotemia, and clinical complications of uremia such as encephalopathy, pericarditis, or neuropathy.

In the ICU, AKI commonly requires expensive supportive therapy, it has high morbidity and it is associated with poor outcomes [1, 7, 9, 12, 19]. The goal of this study was to determine the incidence, causes, risk factors, treatment and outcomes of AKI in critically ill patients in the ICU.

Material and Methods

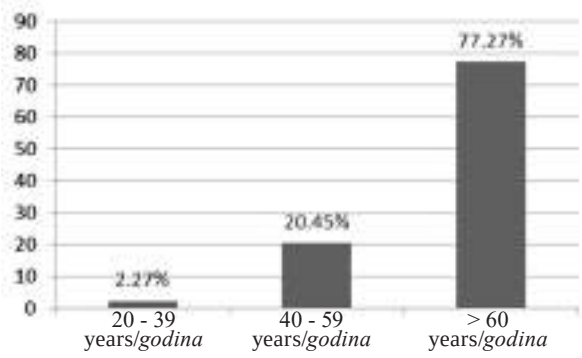
The data of adult patients (older than 18 years of age) admitted to the ICU in 2017 were collected during a three-month prospective study at the Department of Emergency Internal Medicine of the Clinical Center of Vojvodina, Novi Sad. Patients who had at least two measurements of serum creatinine and whose level of serum creatinine was higher than 150 μmol/l were included in the study. Serum creatinine level was followed up during the entire hospitalization.

Demographic data were collected from the medical records including diagnosis on admission to the ICU, complete blood count, biochemistry, comorbidities (diabetes mellitus, arterial hypertension, other cardiovascular diseases, renal disease, prostate diseases, dehydration, burns, gastrointestinal bleeding, pancreatitis, peritonitis, sepsis), the use of nephrotoxic agents (cephalosporins, aminoglycosides, nonsteroidal anti-inflammatory drugs, cytostatics, radiocontrast agents), radiological procedures and treatment of AKI. Patients with chronic renal disease on hemodialysis were excluded from the study. There were no interventions.

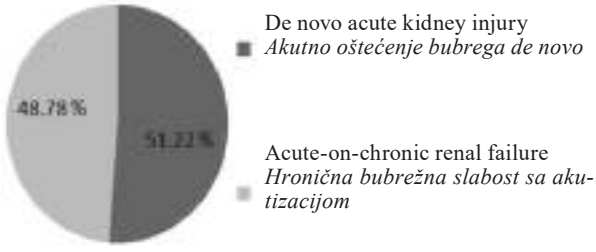
A database was designed for the purpose of this study. All the data were statistically processed and analyzed using appropriate tests. Continuous variables were presented as mean ± standard deviation or median values. Comparison of the analyzed variables was performed by t-test, analysis of variance, Mann-Whitney, Kruskal-Wallis, Wilcoxon as well as χ^2-test. Statistical significance was set at $p < 0.05$.

Results

Of the 220 patients who were hospitalized in the ICU at the Department of Emergency Internal Medicine of the Clinical Center of Vojvodina, Novi Sad, in the period from October to December 2017, 44 patients (20%) were included in the study.



Graph 1. Histogram of age distribution
Grafikon 1. *Histogram distribucije pacijenata u odnosu na starosno doba*



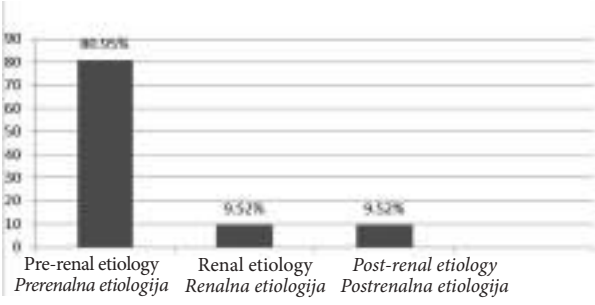
Graph 2. Incidence of de novo AKI and Acute-on-Chronic renal failure
Grafikon 2. *Incidencija de novo akutnog oštećenja bubrega i hronične bubrežne slabosti sa akutizacijom*

The age of patients ranged from 41 to 91 years (mean age 70.09 ± 12.95 years). The median age of patients included in the study was 67 ± 13.20 years (range: 21 to 88). Most patients were older than 60 years, 77.27% (n = 34); 20.45% (n = 9) of patients were aged between 40 to 59 years, and 2.27% (n=1) were aged between 20 to 39 years **(Graph 1)**. The mean age of patients who developed de novo AKI was 67.57 ± 13.30 years and the mean age of patients with acute-on-chronic renal failure was 74.10 ± 10.59 years. The difference in the mean age of patients with de novo AKI and patients with acute-on-chronic renal failure was not statistically significant (p = 0.114) **(Table 1)**.

De novo AKI was found in 51.22% (n = 21) patients and acute-on-chronic renal failure in 48.78% (n = 20) **(Graph 2)**. Among the patients with de novo AKI, 80.95% (n = 17) had a pre-renal AKI, while the same number of patients, 9.52% (n = 2) had intra- and post-renal AKI **(Graph 3)**.

The risk of AKI was increased in patients with comorbidities such as diabetes mellitus, arterial hypertension, other cardiovascular diseases, renal disease, prostate diseases, dehydration, burns, gastrointestinal bleeding, pancreatitis, peritonitis, and sepsis. Among the patients with de novo AKI, 9.52% had a single comorbidity, 28.75% had two and 61.90% of patients had three or more comorbidities. There were no patients without comorbidities. Among the patients with acute-on-chronic renal failure, 10% had two comorbidities and 90% of patients had three or more comorbidities. Likewise, there were no patients without comorbidities and there were no patients with a single comorbidity. The most common comorbidity in patients with de novo AKI was arterial hypertension (52.4%, n = 11), other cardiovascular diseases and sepsis (47.6%, n = 10), and gastrointestinal bleeding (33.3%, n = 7). Among the patients with acute-on-chronic renal failure, the most common comorbidities were cardiovascular disease (90%, n = 18), renal disease (85%, n = 17), arterial hypertension (60%, n = 12), bleeding (50%, n = 10) and diabetes mellitus (40%, n = 8) **(Table 2)**. Comparison of these two groups of patients showed that there was a statistically significantly higher incidence of renal and cardiovascular diseases among patients with acute-on-chronic renal failure ($p < 0.05$).

In the group of patients with de novo AKI, the mean baseline serum creatinine was 315.67 μmol/l, and in patients with acute-on-chronic renal failure it was 272 μmol/l. At the end of hospitalization, the mean serum creatinine was 135.95% μmol/l in patients with de novo AKI and 244.44 μmol/l in the group of patients with acute-on-chronic renal failure. The use of nephrotoxic drugs before and during hospitalization was found in 71.42% of patients with



Graph 3. Etiology of de novo AKI
Grafikon 3. *Etiologija de novo akutnog oštećenja bubrega*

Table 1. Mean age of patients with standard deviation
Tabela 1. *Prosečna starost pacijenata sa standardnom devijacijom*

	Acute kidney injury *Akutno oštećenje bubrega*		Acute-on-chronic renal failure *Hronična bubrežna slabost sa akutizacijom*		
Variable *Parametar*	Mean *Medijana*	Standard deviation *Standardna devijacija*	Mean *Medijana*	Standard deviation *Standardna devijacija*	p/*p*
Age (years)/*Starost* (*godine*)	67.57	13.20	74.10	10.59	0.114

Table 2. Incidence of comorbid diseases in study patinets
Tabela 2. *Incidencija komorbiditeta kod ispitivanih pacijenata*

	De novo acute kidney disease *Akutno oštećenje bubrega de novo*		Acute-on-chronic renal failure *Hronična bubrežna slabost sa akutizacijom*		
	n/*broj ispitanika*	%/*procenat*	n/*broj ispitanika*	%/*procenat*	p/*p*
Diabetes mellitus *Šećerna bolest*	4	19.0	8	40.0	0.141
Arterial hvpertension *Arterijska hipertenzija*	11	52.4	12	60.0	0.623
Renal disease *Bubrežna oboljenja*	4	19.0	17	85.0	<0.001
Cardiovascular diseases *Kardiovaskularna oboljenja*	10	47.6	18	90.0	0.004
Prostate diseases *Bolesti prostate*	2	9.5	4	20.0	0.343
Bleeding/*Krvarenje*	7	33.3	10	50.0	0.279
Burns/*Opekotine*	0	0	0	0	/
Dehidratation/*Dehidratacija*	6	28.6	2	10.0	0.134
Pancreatitis/*Pankreatitis*	4	19.0	1	5.0	0.169
Peritonitis/*Peritonitis*	1	4.8	1	50.0	0.972
Sepsis/*Sepsa*	10	47.6	5	25.0	0.133

de novo AKI and in 40% of patients with acute-on-chronic renal failure.

In the group of patients with de novo AKI, recovery of kidney function was observed in 42.86% (n = 9) of patients. In patients with pre-renal AKI, recovery of kidney function was found in 47.1% (n = 8) and in patients with post-renal AKI it was found in 50% (n = 1). There were no patients with kidney function recovery among those who had renal etiology of AKI.

In-hospital mortality was 28.57% (n = 6) in the group of patients with de novo AKI and 50% (n = 10) among patients with acute-on-chronic renal failure. This result was statistically significant (p = 0.004).

De novo AKI was treated conservatively in 90.48% (n = 19) of patients and 9.52% (n = 5) of patients received renal replacement therapy **(Graph 4)**.

Discussion

Acute kidney injury is a common and serious complication in critically ill patients in the ICUs [1, 3, 12]. It is associated with increased risk of in-hospital mortality and long-term chronic kidney disease. The rapid increase in aging population with multiple comorbidities contributes to high incidence of AKI. The aim of this study was to determine the etiology of AKI (pre-renal, renal or post-renal cause). Risk factors for AKI are old age, chronic kidney disease as well as comorbidities such as diabetes mellitus, hypertension and cardiovascular disease. The treatment of AKI should begin by hemodynamic stabilization, identification of complications (hyperkalemia, metabolic acidosis, anemia and fluid overload) and the cause of AKI. If conservative treatment appears not to be effective enough, RRT needs to be considered. In the ICU, AKI frequently requires expensive supportive therapy, it has high morbidity and poor outcome. The objective of this study was also to determine the incidence, causes, risk factors, treatment and outcomes of AKI in critically ill patients in the ICU.

Graph 4. Treatment of de novo AKI
Grafikon 4. *Lečenje de novo akutnog oštećenja bubrega*

The study included 44 patients who were hospitalized in the ICU at the Department of Emergency Internal Medicine of the Clinical Center of Vojvodina in Novi Sad during 3 months in 2017. The median age was 67 ± 13.20 years and most patients were older than 60 years, 77.27%. Similar results were obtained in other studies [1, 12]. In these studies, patients with AKI were over 60 years of age and the median age was 64 years.

De novo AKI was diagnosed in 51.22% of patients and acute-on-chronic renal failure in 48.78%. In 2021, the study of Picckers et al. showed that the incidence of AKI in critically ill patients was from 30% to 60%. Jiang et al. also reported AKI incidence of 50% in critically ill patients [3, 12]. The most common etiology of de novo AKI was pre-renal, in 80.95% of patients. Similar results were obtained by Kellum et al., showing that the main causes of AKI were dehydration, hypotension and shock (77 %) [12].

The risk of AKI is increased in patients with comorbidities such as diabetes mellitus, arterial hypertension, other cardiovascular diseases, renal disease, prostate diseases, dehydration, burns, gastrointestinal bleeding, pancreatitis, peritonitis, and sepsis. Out of 21 patients with de novo AKI, 61.9% had three or more

comorbidities, 28.75% had two and 9.52% had one comorbidity. There were no patients without comorbidities. Patients with acute-on-chronic renal failure had three or more comorbidities in 90% of cases and 10% had two comorbidities. In this group, there were also no patients without comorbidities. The most common comorbidity in patients with de novo AKI was arterial hypertension, in 52.4%, other cardiovascular diseases and sepsis were present in 47.6% of patients and gastrointestinal bleeding was present in 33.3% [1]. Among the patients with acute-on-chronic renal failure, the most common comorbidities were cardiovascular disease (90%), renal disease (85%), arterial hypertension (60%), bleeding (50%) and diabetes mellitus (40%). Numerous studies show that comorbidities are a significant risk factor for AKI [1, 2, 12], which is in agreement with our results. Use of nephrotoxic drugs before and during hospitalization was found in 71.42% of patients with de novo AKI and in 40% of patients with acute-on-chronic renal failure. Similar results were obtained in other studies [2, 12]. Gameiro et al. reported that the use of nephrotoxic drugs is associated with 20 – 40% of cases of AKI and in up to 60% in elderly patients. These results are similar to the results of our study. Kellum et al. showed that risk for AKI increases with the number of nephrotoxic drugs used.

In the group of patients with de novo AKI, 42.86% recovered the kidney function. In the group of patients with pre-renal AKI, 47.1% recovered the kidney function, and in the group of patients with post-renal AKI, 50% recovered the kidney function. There were no patients who recovered the kidney function among those who had renal etiology of AKI. Some studies that evaluated recovery from all forms of AKI (including less severe forms) reported complete recovery rates between 33% and 90% [20].

In-hospital mortality was 28.57 % in the group of patients with de novo AKI and 50% among patients with acute-on-chronic renal failure. The mortality rate in patients with acute-on-chronic renal failure was statistically significantly higher than in patients with de novo AKI. This can be explained by the older age and multiple comorbidities in these patients. Our results are in agreement with the results of Kellum et al. reporting a mortality rate of 23%. This study showed that the mortality rate reached 49.4% in patients on RRT [12, 17, 18].

De novo AKI was treated conservatively in 90.48% of patients, while 9.52% of patients received RRT. The most common treatment was conservative and supportive. It started by hemodynamic stabilization and early identification of the cause and complications of AKI. Nephrotoxic drugs were discontinued and the dose of other drugs was adjusted according to the renal function. In cases when conservative treatment did not show good results in treating complications of AKI, such as hyperkalemia, metabolic acidosis, anemia, and fluid overload, RRT was initiated [2, 17, 18]. Early initiation of RRT can allow better control of metabolic abnormalities and other complications associated with increased mortality. Although it is life-saving in many situations, RRT may be associated with iatrogenic complications (hypotension, bleeding, infection, or hypothermia). The appropriate timing of RRT initiation has been the subject of many studies [17, 18].

Conclusion

The results of this study showed that de novo acute kidney injury was found in approximately half of the critically ill patients in the intensive care unit. The most frequent etiology was pre-renal. Acute kidney injury was mainly detected in older patients with comorbidities. The most common comorbidities were arterial hypertension, other cardiovascular diseases and sepsis. During hospitalization, most patients were treated conservatively. Old age and comorbidities were associated with poor outcome and high mortality.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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CHRONIC HEPATITIS C AND HEREDITARY HEMOCHROMATOSIS – A CASE REPORT

HRONIČNI HEPATITIS C I HEREDITARNA HEMOHROMATOZA – PRIKAZ SLUČAJA

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Summary

Introduction. Between 20 – 60% of patients with chronic hepatitis C present with elevated serum ferritin and iron, as well as increased transferrin saturation, yet without a significant liver iron burden. The objective of this article was to summarize current knowledge on interactions between hepatitis C virus infection and iron metabolism. **Case Report.** A 34-year-old female patient positive for hepatitis C virus genotype 3, underwent therapy of chronic hepatitis C with pegylated interferon/ribavirin. The therapy was discontinued after four weeks due to leukopenia, anemia and significantly increased ferritin levels. Liver biopsy (Perl's stain) revealed iron deposition predominantly in periportal hepatocytes. The therapy of chronic hepatitis C was continued by direct-acting (sofosbuvir/antiviral/velpatasvir) drugs. During the course of the therapy, the patient presented with normal complete blood count, ferritin of 150 μg/l, and ferremia at upper limit of normal. Twelve weeks after the end of the therapy, the patient showed a sustained virologic response. The additional diagnostics of hereditary hemochromatosis has been performed, and therapeutic phlebotomy procedures were initiated. **Conclusion.** In patients with chronic hepatitis C and significantly elevated serum ferritin and iron, the diagnosis should be extended to hereditary hemochromatosis.

Key words: Hepatitis C, Chronic; Hemochromatosis; Iron Overload; Ferritins; Diagnosis; Interferons; Antiviral Agents; Phlebotomy; Treatment Outcome

Sažetak

Uvod. Kod 20−60% pacijenata sa hroničnim hepatitisom C postoji povećanje vrednosti serumskog feritina i gvožđa, kao i povećana saturacija transferina, bez značajnog opterećenja jetre gvožđem. Cilj rada je da se sumiraju dosadašnja saznanja o interakcijama hepatitis C virusne infekcije i poremećaja metabolizma gvožđa. **Prikaz slučaja**. Kod bolesnice stare 34 godine, pozitivne na hepatitis C virus, genotip 3, započeto je lečenje hroničnog hepatitisa C kombinacijom pegilovani interferon/ribavirin. Zbog leukopenije i anemije, uz perzistiranje značajno povišenih vrednosti feremije i feritina, ova terapija je ukinuta nakon četiri nedelje. Biopsijom jetre, bojenjem po Perlsu, ustanovljena je pozitivna depozicija gvožđa dominantno u hepatocitima periportnih prostora. Lečenje hroničnog hepatitisa C nastavljeno je primenom direktno delujućih antivirotika (sofosbuvir/velpatasvir). Tokom terapije bolesnica je imala normalnu kompletnu krvnu sliku, feritin 150 μg/l, a feremija je bila na gornjoj granici normale. Dvanaest nedelja od završetka terapije bolesnica je postigla trajni virološki odgovor. Sprovedena je dodatna dijagnostika hereditarne hemohromatoze i započete su terapijske flebotomije. **Zaključak**. Kod bolesnika sa hroničnim hepatitisom C i značajno povećanim serumskim feritinom i gvožđem potrebno je proširiti dijagnostiku u pravcu nasledne hemohromatoze.

Ključne reči: hronični hepatitis C; hemohromatoza; preopterećenje gvožđem; feritini; dijagnoza; interferoni; antivirusni lekovi; flebotomija; ishod lečenja

Introduction

Iron is an essential element in a wide range of physiological processes. Excessive amounts of iron may have toxic effects by generating oxidative stress and reactive oxygen radicals, thereby causing oxidation of lipids, proteins, and nucleic acids. This can aggravate the liver damage in a variety of non-hemochromatosis chronic liver diseases. Elevated serum levels of ferritin and iron are found in 20 – 60% of patients with chronic hepatitis C (CHC) [1].

The hepatitis C virus (HCV) upregulates the hepcidin antimicrobial peptide gene expression; the virus has the ability to control iron levels in order to achieve more efficient replication and persistence via both intracellular iron sequestration and intracellular iron mobilization mediated by hepcidin and ferritin, respectively [2, 3].

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Abbreviations

HFE gene	– hemochromatosis gene
HCV	– hepatitis C virus
CHC	– chronic hepatitis C
HH	– hereditary hemochromatosis
PEG IFN/RBV	– pegylated interferon/ribavirin
METAVIR	– meta-analysis of histological data in viral hepatitis
RNA	– ribonucleic acid
PCR	– polymerase chain reaction
ALT	– alanine aminotransferase
ULN	– upper limit of normal
DAA	– direct-acting antiviral
SVR	– sustained virologic response
CBC	– complete blood count

Iron metabolism disorder in CHC patients is a factor contributing to accelerated development of liver fibrosis, and is associated with poor therapeutic response to combined pegylated interferon/ribavirin antiviral (PEG IFN/RBV) therapy [4–6].

Hereditary hemochromatosis (HH) is a hereditary disorder characterized by increased intestinal absorption of dietary iron and consequent excessive iron deposition in various organs. The prevalence of HH in Northern Europe is 1 per 202 – 250 individuals. About 85 – 90% of patients with HH are homozygous for the C282Y hemochromatosis (HFE) gene mutation, whereas about 10 – 15% of patients have H63D mutation. Phenotypic expression occurs in about 70% of C282Y homozygotes [7].

The objective of this article was to summarize current knowledge on interactions between HCV infection and iron metabolism disorders by presenting a case of a female patient with HCV infection and HH.

Case Report

At the end of 2019, a 34-year-old female patient consulted an infectious disease specialist for the first time, although she had known about hepatitis C infection since 2008.

Quantitative HCV ribonucleic acid (RNA) polymerase chain reaction (PCR) test confirmed viremia (298.673 IU/ml), HCV genotype 3, and liver ultrasound elastography was performed showing 6.8 kPa. The patient underwent combined PEG IFN/RBV therapy at the expense of the Republic Fund of Health Insurance of Serbia.

During the course of the therapy, extremely elevated serum levels of iron (64.5...44 μmol/l) and ferritin (2530...1055 μg/l) were observed with alanine aminotransferase (ALT) levels being four times higher than the upper limit of normal (ULN). Transferrin saturation values were 96% and 81% at the first and second blood sampling, respectively **(Table 1)**. A gastroenterohepatologist was included into the team for further monitoring.

In February 2020, a liver biopsy was performed. Perl's stain revealed positive iron deposition predominantly in the hepatocytes of the periportal space. The meta-analysis of histological data in viral hepatitis (METAVIR) scoring showed grade 2 fibrosis and grade 1 activity. Quantitative liver iron measurement in dry liver tissue was not performed due to technical reasons. The finding clearly suggested hemochromatosis.

In March 2020, blood analysis revealed leucopenia 1.97 (10^9/l) with absolute neutrophil count 0.67 (10^9/l), and anemia erythrocyte 3.29 (10^{12}/l) hemoglobin 110 g/l. Ferremia and ferritin values were 44 μmol/l and 1055 μg/l, respectively. The ALT showed a decreasing tendency, but still remained elevated, being 20% above the ULN. Considering the laboratory and histopathological results of the liver biopsy, a decision on discontinuation of PEG IFN/RBV therapy was made.

In May 2020, a molecular-genetic examination using PCR-Restriction Fragment Length Polymorphism (-RFLP) lab-on-a-chip electrophoresis from the buccal mucosa swab was performed in order to confirm hemochromatosis. Genetic analysis revealed that the patient was homozygous for the *C282Y* hemochromatosis gene mutation. The H63D mutation was not detected in this patient.

During July, August and September 2020, the patient underwent therapy for HCV infection (genotype 3) using direct-acting antiviral (DDA) drugs, a combination of sofosbuvir/velpatasvir (SOF/VEL) over a 12-week period. During the therapy, the patient had normal complete blood count (CBC), ferritin of 150 μg/l, and ferremia at ULN.

Table 1. Metabolic parameters for iron, ALT and therapeutic management in the study period
Tabela 1. *Vrednosti parametara metabolizma gvožđa, ALT i terapija bolesnice u periodu studije*

Month/Year *Mes./god.*	Fe* (μmol/l)	Ferritin* (μg/l)	Transferrin* (g/l)	Transferrin saturation *Sat. transf.* (%)	ALT U/l	Therapy *Terapija*
Jan. 2020	64.5	2530	2.68	96	158	PEG IFN/RBV
Mar. 2020	44	1055	2.17	81	52	PEG IFN/RBV
Sept. 2020	30	150	/	/	/	Sofosbuvir/Velpatasvir
Sept. 2021	40	226	/	/	/	therapeutic phlebotomy/*terapijska flebotomija*
Sept. 2021	44.8	481	1.9	94	26	hematemesis management/*lečenje hematemeze*
Nov. 2021	46.9	1022	/	/	35	therapeutic phlebotomy/*terapijska flebotomija*

Legend: Fe – ferremia (n 9 - 30 μmol/l); Ferritin (n 10 - 120 μg/l); Transferrin (n 1.8 - 3.6 g/l); Transferrin saturation (n 15 - 50%); ALT – alanine aminotransferase (n 5 - 48 U/l)
Legenda: Fe – feremija (n 9 - 30 μmol/l); Feritin (n 10 - 120 μg/l); Transferin (n 1,8 - 3.6 g/l); Sat. transf. – Saturacija transferina (n 15 - 50%); ALT – alanin aminotransferaza (n 5 - 48 U/l); PEG IFN/RBV – pegilovani interferon/ribavirin

Twelve weeks after completing the therapy, the patient's status was confirmed as PCR RNA HCV negative.

The echocardiography finding was normal and the thyroid gland hormone values were within the reference range. The patient was diagnosed with type 2 diabetes mellitus (T2DM), and metformin 850 mg/day was introduced into the therapeutic protocol. Tumor marker results (Ca 19-9, Ca 125, AFP, and CEA) showed no deviation from the reference ranges. The gynecological finding was normal, except for one episode of menometrorrhagia, which was managed by norethisterone. Psychiatric examination revealed an acute reaction to stress.

In September 2021, ferremia and ferritin values were 40 μmol/l and 226 μg/l, respectively, and ALT was 26 **(Table 1)**. Therapeutic phlebotomies were introduced. At first phlebotomy, 300 ml blood was removed and replaced with the same volume of saline solution.

A day after therapeutic phlebotomy, the patient had hematemesis. Endoscopy revealed reflux esophagitis grade C, a small sliding hiatal hernia, and esophageal moniliasis. During the hospital treatment, there were no significant blood count impairments; ferremia was 44.8 μmol/l, with ferritin and transferrin values of 481 μg/l and 1.9, respectively. Transferrin saturation was 94% **(Table 1)**. Considering the gastrointestinal bleeding, therapeutic phlebotomy was not performed during the period of hospitalization.

In November 2021, the examination revealed ferremia of 46.9 μmol/l, ferritin 1022 μg/l, and ALT 35. A second therapeutic phlebotomy was performed. Further follow-up examinations as well as phlebotomies were planned.

Discussion

In this article, we presented a case of a female patient undergoing CHC therapy and presenting with elevated values of serum iron and ferritin. Accordingly, liver biopsy and genetic testing for HH were performed.

Arber et al. reported that serum iron increase may occur in some 36% of all chronic liver diseases as a non-specific consequence of liver necroinflammation. They observed that CHC patients manifest with elevated serum iron and transferrin saturation, yet without excessive liver iron accumulation. A likely explanation of this phenomenon is the release of iron from damaged inflamed liver cells due to cytopathic nature of HCV activity [8].

Sebastiani and Walker reported stainable hepatic iron deposits in 3 – 38% of patients with CHC. Many patients with CHC who manifest with either elevated serum ferritin or increased transferrin saturation, or both, do not present with a significant increase in hepatic iron content [1].

Considering overly restrictive criteria for DAA-therapy of CHC (covered by the Republic Fund of Health Insurance of Serbia), our patient underwent therapy (based on a relevant pre-treatment protocol) with a combination of PEG IFN/RBV; however, due to substantial leucopenia and moderate anemia, as well as persistent significantly elevated ferremia and ferritin values, the therapy was discontinued four weeks later. Increased iron and ferritin values were considered to be the consequence of HCV-induced cytopathic effect on hepatocytes, and partly attributed to the therapy itself.

Some authors recommend control of iron status and therapeutic phlebotomy prior to interferon therapy, as well as in case of a lack of therapeutic response, though with somewhat conflicting results [9–11].

Taking into consideration the transaminase activity accompanied with increased ferremia and ferritin values, the next diagnostic step was liver biopsy aimed at confirming or excluding HH. Histopathological analysis of the liver biopsy (Perl's stain) revealed presence of iron in periportal hepatocytes and a METAVIR scoring of grade 2 fibrosis and grade 1 activity. The distribution of iron deposits in the liver suggested hemochromatosis.

The iron stain in the liver biopsy is not rare; however, histopathological pattern identified by Brunt et al., indicates the probability of iron overload in HH, the so called HFE-related iron overload. In HH, iron deposition is dominantly observed in periportal hepatocytes (acinar zone 1) with a decreasing gradient towards zones 2 and 3. In case of heavy iron accumulation, the deposits can extend to Kupffer cells, bile duct epithelium and fibrous tissue.

At initial stages of iron deposition (in other diseases), the iron accumulates preferentially in sinusoidal lining cells showing diffuse distribution within the acinus. Panacinar activity of Kupffer cells and portal macrophages is observed, such as in CHC [12].

Ikura et al. reported a positive correlation between iron deposition within the portal space and hepatic inflammation activity and fibrosis grade, as well as its negative correlation with response to INF-therapy in patients with CHC [13].

Genetic analysis revealed that the patient was homozygous for the *C282Y* hemochromatosis gene mutation, and thus, along with pronounced biochemical characteristics such as high ferritin (> 1000 μg/l) and iron values, strongly indicated HH. The finding of iron in periportal hepatocytes confirmed the diagnosis of HH. The determined grade 2 fibrosis could suggest potential accelerated fibrosis considering that the patient was a younger age female with HCV infection caused by genotype 3.

The obtained results correspond with studies reporting that CHC patients carrying C282Y mutation have increased serum iron indices, frequent iron depositions in the liver and progressive fibrosis and cirrhosis, contrary to patients without C282Y mutation. This is particularly pronounced in CHC associated with genotype 3, which is characterized by high prevalence of hepatic iron deposits [14–17].

Conversely, a multicentric study carried out in Norway established similar values for ferritin and transferrin saturation in HCV patients with C282Y mutation, and HCV positive patients without the mutation,

whereas liver fibrosis and hepatic iron deposition were independent from C282Y mutation [6].

Hofer et al. established that hepatic iron content and therapeutic response in CHC patients are not related with the presence or absence of HFE gene mutation. They reported that serum ferritin in CHC patients reflects the inflammation and advanced fibrosis rather than hepatic iron overload. Since hepatic iron content does not affect the treatment response of PEG IFN/RBV in CHC, the authors believe that phlebotomy prior or during therapy is of no significant benefit to patients [18].

In the patient described in this article, after establishing the diagnosis of HH with apparent side effects of PEG IFN/RBV, the possibility of repeated therapy with the same drugs was excluded. In the further course of the disease, the patient underwent a DAA therapy protocol including sofosbuvir/velpatasvir during 12 weeks. Throughout the treatment period, the patient had normal CBC, ferritin of 150 μg/l, and ferremia at ULN. Twelve weeks after completing the therapy, the patient has achieved a sustained virologic response (SVR) and a PCR RNA HCV negative status.

Chang et al. reported that in DAA-treated SVR CHC patients, ferritin levels decreased and remained stable at 24 weeks post therapy [19].

Nine months after achieving SVR, our patient presented with ferremia 40 of μmol/l, and ferritin of 226 μg/l. In regard to the diagnosis of HH, the decision on starting phlebotomy treatment was made.

Serum ferritin levels recorded during the monitoring period indicated initial dual effects of two factors – CHC and HH. During the DAA therapy, significant improvement of serum ferritin and iron was observed. Afterwards, the values continued to gradually increase and remained persistently elevated, though lower than those recorded in the period when both etiological factors were present. All this suggests that the changes may be attributed to HH.

The monitoring of all distinct clinical elements indicating HH and timely treatment of potential disorders was intended.

Conclusion

In patients with chronic hepatitis C and significantly increased levels of serum ferritin and iron, the diagnosis should be extended to confirm or exclude hereditary hemochromatosis. The coexistence of chronic hepatitis C and hereditary hemochromatosis indicates the use of direct-acting antiviral drugs as the initial treatment, followed by therapeutic phlebotomy procedures.

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Case report
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A RARE CASE OF CYANIDE INTOXICATION

REDAK SLUČAJ TROVANJA CIJANIDOM

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Summary

Introduction. Cyanide is one of the most rapidly acting poisons and therefore it can be important in cases of suicide, homicide or accidental death. Nevertheless, cyanide intoxications are not common in forensic practice. **Case Report.** We present a case of a Caucasian male, 63 years of age, whose body was found lying in bed in his cottage by the river. A gun was found on the bedside table. Three glass bottles were found under the bed containing a liquid and crystalline substance. On autopsy, there were pathological changes in the heart, but the circumstances of the case were not in line with these findings. **Conclusion.** Sometimes, autopsy and routine toxicological analysis cannot solve the case, so it is necessary to pay special attention to unusual substances found at the scene. In such cases, all samples taken during the autopsy should be stored appropriately, in case an additional, a specific toxicological analysis is required. In this particular case, after obtaining the results of specific toxicological analysis, it was determined that it was a suicide by cyanide poisoning.

Key words: Cyanides; Autopsy; Forensic Medicine; Forensic Toxicology; Poisoning; Suicide

Sažetak

Uvod. Cijanid predstavlja jedan od najbrže delujućih otrova i zbog toga može biti od značaja u slučajevima samoubistava, ubistava ili zadesnih smrti. Uprkos tome, trovanje cijanidom nije čest slučaj u sudskomedicinskoj praksi. **Prikaz slučaja.** Predstavljamo slučaj osobe muškog pola, starosti 63 godine, pronađene u krevetu u ležećem položaju, u njegovoj vikendici pored reke. Na noćnom stočiću, pored kreveta, pronađen je pištolj. Ispod kreveta pronađene su tri staklene bočice, u kojima se nalazio sadržaj tečnog i čvrstog agregatnog stanja. Tokom obdukcije nađene su patološke promene na srcu, ali okolnosti slučaja nisu bile u skladu sa ovim nalazima. **Zaključak.** Ponekad obdukcija i rutinske toksikološke analize ne mogu da razreše slučaj, te je potrebno obratiti posebnu pažnju na prisustvo neuobičajenih supstancija na licu mesta. U takvim slučajevima, svi uzorci uzeti tokom obdukcije bi trebalo da se čuvaju na odgovarajući način, u slučaju potrebe za dodatnim, to jest, specifičnim toksikološkim analizama. Nakon dobijanja rezultata specifičnih toksikoloških analiza, u konkretnom slučaju utvrđeno je da se radi o samoubistvu, uzrokovanom trovanjem cijanidima.

Ključne reči: cijanidi; autopsija; forenzička medicina; forenzička toksikologija; trovanje; samoubistvo

Introduction

Cyanide is one of the most rapidly acting poisons. It is highly toxic and therefore it can be important in cases of suicide, homicide or accidental death. It is found in the form of salts, such as potassium cyanide (KCN) and sodium cyanide (NaCN) and in the form of hydrogen cyanide (HCN), also known as prussic acid. Most of the cyanide salts are used in gold mining where they are mainly used to extract precious metals in the mining industry, in organic synthesis, metallic luster industries, and electroplating and fumigation. It is also used in jewelry processing for refining gold and silver by chemical gilding and buffing [1]. A small amount of cyanide is present in the seeds of bitter almond and in stone fruits like apricots and peaches [2]. Hydrogen cyanide is a component of vehicle exhaust, tobacco smoke and combustion products of natural and synthetic materials [3].

Low levels of cyanide may be found in healthy persons, due to normal metabolism, after eating certain fruits or in smokers. Cyanide levels in normal red blood cells may be < 0.026 mg/L. In healthy volunteers, endogenous cyanide concentrations are approximately 0.0084 ± 0.0039 mg/L, while in whole blood samples of smokers the cyanide levels are ≥ 0.5 mg/L [4]. The minimal lethal dose of HCN for an adult is around 100 mg. The minimal lethal dose of KCN is around 200 mg [5]. Cyanide may be fatal at plasma concentrations of 0.26 mg/L and above. The toxic concentration is 0.50 mg/L, lethal concentrations are 4 to 5 mg/L, but also reported to be as low as 1 mg/L [4]. In children, the lethal concentration is even lower. Regardless of the way of administration, after it is absorbed, cyanide binds a mitochondrial enzyme, cytochrome oxidase. This leads to anaerobic respiration, accumulation of lactate, metabolic acidosis, respiratory failure, coma and death.

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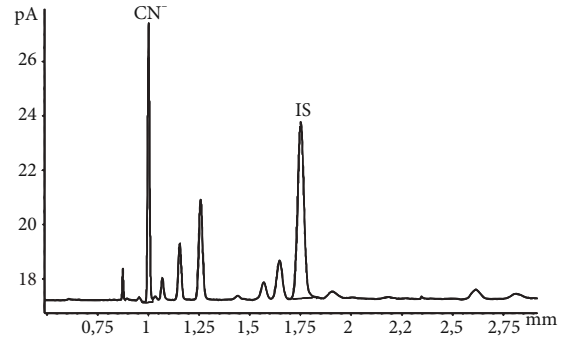
Abbreviations
KCN – potassium cyanide
BAC – blood alcohol concentration

Case Report

A body of a Caucasian male, 63 years of age, was found lying in bed, in his cottage by the river. A gun was found on the bedside table and three glass bottles were found under the bed **(Figure 1)**. A liquid content was found in two and a crystalline substance in the third bottle. The body was transported to our forensic institution for an autopsy.

The external examination showed that the deceased was 161 cm in height, well nourished, with poor muscular build. The face and conjunctivae were pale and no petechial hemorrhage was found. There were no signs of mechanical trauma. The internal examination showed pulmonary and brain edema, and congestion of internal organs. The heart weight was 440 g, the left ventricular wall thickness was 2,2 cm and the right ventricular wall thickness was 0,5 cm. There was a mild atherosclerosis of coronary arteries with no other macroscopic pathological findings. The stomach mucosa was unremarkable and there was a certain amount of semi-digested food. It was noticed that the blood was bright red in color. Microscopic findings were nonspecific, revealing only mild fibrosis of the myocardium and brain and pulmonary edema. Since the autopsy findings revealed no marked pathological changes, biological samples were taken for toxicological analysis. For the routine toxicological analysis, samples of gastric content, femoral arterial blood, urine and bile were screened for different drugs and pharmaceuticals by standard procedures using gas chromatography mass spectrometry (GC-MS), and blood was also examined for ethanol by headspace method using gas chromatography with flame ionization detector (HS–GC/FID) [6]. Toxicological examination revealed no common drugs and pharmaceuticals in samples, with blood alcohol concentration (BAC) of 40 mg/L (0.04 mg/ml) **(Graph 1)**.

Figure 1. Glass bottles found under the bed containing a liquid and crystalline substance
Slika 1. *Staklene boce pronađene ispod kreveta sa sadržajem tečnog i čvrstog agregatnog stanja*



Graph 1. Gas chromatography with flame ionization detector chromatogram of the blood sample showing cyanide retention time and internal standard
Grafikon 1. *Hromatogram gasne hromatografije sa plamenojonizujućom detekcijom uzorka krvi, koji pokazuje vremena zadržavanja za cijanid i interni standard*

About two months later, an information was found about a written letter that looked like a suicide note and the police investigation revealed that the deceased was an owner of a jewelry store. Having this in mind, it was clear that he had easy access to cyanide salts. As a jeweler, he could have used it for refining precious metals, such as gold and silver and he knew the toxicity potential of cyanide. Considering these circumstances, a case of suicide by cyanide poisoning was suspected and specific toxicological analysis of the remaining stored samples was performed.

Before the analysis of the remaining biological samples, liquid and crystalline contents of three small glass bottles found under the bed at the scene were tested for cyanide by Prussian blue [7] spot formation, and presense of cyanide was confirmed. The remaining samples of femoral arterial blood and gastric content were then analyzed by headspace method using gas chromatography with flame ionaization detector and revealed cyanide concentration of 7.47 mg/L and 206 mg/L, respectively.

The weapon expertise of the gun found on the bedside table showed that the gun was not fired. Since the autopsy did not show any specific findings, nor did the routine toxicological analysis reveal significant information regarding the cause of death (BAC 40 mg/L), the specific toxicological analysis determined the cause of death to be suicide by cyanide poisoning.

Discussion

Cyanide intoxications are not very common in forensic practice. A five-year survey which included 700 cases of suicide by all methods, revealed only 6 cases of cyanide intoxication [8]. In cases of suicide by cyanide, the most commonly used are cyanide salts dissolved in liquid (water or beer) so a glass or a beer bottle with white powder residue can be found at the scene. A death by injection of cyanide was also reported [9]. A syringe and a needle were found in bed, beside the body. It is not an interesting case just because of the way the cyanide was administered, but it also

showed that cyanide may be used to commit homicide. In this case, the perpetrator entered through the window while the victim was asleep, and stuck a needle into the victim's abdomen. The fact that certain fruits may be potentially dangerous for cyanide intoxication is shown by a report of a woman with carcinoma of the large bowel, who ingested 12 bitter almonds and collapsed about 15 minutes later [10]. In this case, thanks to rapid medical intervention, she survived. Cyanide intoxication can be caused by inhalation of toxic fumes and smoke during fires, especially in small, confined spaces, such as a car [11]. In one case the deceased was locked inside a car with a cooking pot that contained dark blue crystals. Some elements found on autopsy and toxicology analysis showed that there was also a concurrent oral ingestion of potassium cyanide.

In our population, the leading causes of intoxication are medications, pesticides, herbicides and corrosive substances. According to a conducted study on attempted and committed suicides with rodenticides, the most frequently used substances, in 85 cases of attempted suicide, were zinc phosphide and rat poison, while zinc phosphide was the only substance used in all 3 cases of committed suicides [12]. Another study showed that, when it comes to corrosive substances, the most commonly used are sodium hydroxide and hydrochloric acid [13]. Cyanide poisoning in our country is extremely rare. In our case, the smell of bitter almond, which is specific for cyanide, was not registered on autopsy. It is not uncommon to miss this smell, because cyanide does not always give off an odor and the ability to smell cyanide is inherited, so there is a wide range of sensitivity in the population and a significant percentage of people cannot detect the smell [9, 14]. On the other hand, the toxicology results were unambiguous. The determined cyanide concentration in the blood sample of 7.47 mg/L was far above the minimal lethal concentration [4]. The concentration of 206 mg/L that was found in the gastric content was in line with the concentrations reported in some other articles [2]. These concentrations were determined after acquiring the results of a specific toxicological analysis, because biological samples were not routinely analyzed for cyanide and it was necessary to perform a specific toxicological analysis. Concentrations of cyanide can change post mortem due to rapid diffusion, so the samples should be taken and analyzed as soon as posible after death. If not, it is suggested that the samples must be stored in a freezer [15]. In our case, the specific toxicological analysis for cyanide was done about two months after the autopsy and the samples were stored as mentioned.

Conclusion

In this study, the authors emphasized the importance of a thorough investigation and detailed documentation of the crime scene. Sometimes, autopsy and routine toxicological analysis cannot solve the case, so it is necessary to pay special attention to unusual substances found at the scene. All samples should be stored appropriately, in case an additional, specific toxicological analysis is required. It must also be emphasized that, due to the high toxicity of cyanide, although the chances are small, urgent and adequate medical help may save the poisoned person's life.

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ACINETOBACTER SUPERINFECTION IN ELDERLY COVID-19 PATIENTS WITH PNEUMOTHORAX – A REPORT OF TWO CASES

SUPERINFEKCIJA ACINETOBACTEROM KOD STARIJIH COVID-19 PACIJENATA SA PNEUMOTORAKSOM - PRIKAZ DVA SLUČAJA

Džemail S. DETANAC[1], Dženana A. DETANAC[1], Dragan STOJKOVIĆ[2] and Lejla ĆERANIĆ[1]

Summary

Introduction. Coronavirus disease 2019 is an infectious disease that primarily affects the lungs. Since the pandemic of severe acute respiratory syndrome coronavirus 2 continues and a large number of cases are registered worldwide, the knowledge about the virus and virus-related complications is growing as well. Pleural complications, pneumothorax, and empyema are important issues affecting better patient survival. Bacterial superinfections may cause complications of coronavirus disease 2019. Knowledge about the incidence of superinfections, microbiological causes, treatment, and outcomes of the disease is incomplete. **Case Report.** We present two oxygen-dependent patients with coronavirus disease 2019 who developed pneumothorax and empyema during hospitalization, three weeks after the onset of coronavirus disease 2019 symptoms. Multidrug-resistant Acinetobacter spp. was isolated from the thoracic drain. **Conclusion.** Pneumothorax may occur at any stage of coronavirus disease 2019 and is not always associated with the severity of viral infection. Empyema due to coronavirus disease 2019 pneumonia is rare and occurs as a superinfection of the pleural effusion. Excessive use of antibiotics in the treatment of hospitalized patients with coronavirus disease 2019 may increase the risk of nosocomial infections caused by multidrug-resistant bacteria.

Key words: COVID-19; Pneumothorax; Empyema; Pleural Effusion; Superinfection; Acinetobacter; Anti-Bacterial Agents; Drug Resistance, Bacterial; Risk Factors; Cross Infection

Sažetak

Uvod. Koronavirusna bolest 2019 je infektivna bolest koja prvenstveno pogađa pluća. Kako se pandemija teškog akutnog respiratornog sindroma *Coronavirus* 2 nastavlja i registruje veliki broj slučajeva širom sveta, znanje o samom virusu raste, kao i saznanje o komplikacijama. Pleuralne komplikacije, pneumotoraks i empijem važna su pitanja u vezi sa boljim preživljavanjem pacijenata. Bakterijske superinfekcije mogu zakomplikovati COVID-19. Saznanja o učestalosti superinfekcija, mikrobiološkim uzročnicima, lečenju i ishodu bolesti su nepotpuna. **Prikaz slučajeva.** Predstavljamo pacijente obolele od kovida, na kiseoničkoj terapiji, kod kojih se razvio pneumotoraks i empijem tokom hospitalizacije, nakon tri nedelje od početka simptoma infekcije koronavirusne bolesti 2019. Multirezistentni *Acinetobacter spp.* izolovan je iz brisa torakalnog drena. **Zaključak.** Pneumotoraks se može pojaviti u bilo kojoj fazi COVID-19 i nije uvek povezan sa težinom virusne infekcije. Empijem zbog COVID-19 pneumonije je redak i javlja se kao superinfekcija pleuralnog izliva. Prekomerna upotreba antibiotika u lečenju hospitalizovanih pacijenata sa COVID-19 može povećati rizik od bolničkih infekcija uzrokovanih multirezistentnim bakterijama.

Ključne reči: COVID-19; pneumotoraks; empijem; pleuralni izliv; superinfekcija; Acinetobakterija; antibiotici; bakterijska rezistencija na lekove; faktori rizika; unakrsna infekcija

Introduction

Over the last two years, since it was discovered in China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spreading rapidly around the world and is a major health problem even in the most advanced health systems. As the number of case studies about all types of SARS-CoV-2 and coronavirus disease 2019 (COVID-19) increases, so is the knowledge about the specifics of this disease and its complications [1]. The symptoms of COVID-19 typically include the respiratory system, but sometimes they present with abdominal pain, without findings of abdominal disease, and with no respiratory symptoms. Patients with diabetes, heart disease, hypertension, obesity, malignant diseases, and the elderly are at a greater risk of developing a severe clinical picture with complications [1–3].

The clinical symptoms in patients with COVID-19 pneumonia may range from asymptomatic to respiratory failure. The COVID-19 pneumonia may be complicated by pneumothorax, pleural effusion, pneumomediastinum, and empyema. Pneumothorax may be spontaneous, or it can be caused by barotrauma in patients on mechanical ventilation. Empyema due to COVID-19 pneumonia is rare and

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COVID-19	– coronavirus disease 2019
SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
RT-PCR	– reverse transcription polymerase chain reaction
CT	– computed tomography
HFNO	– high-flow nasal oxygen
IV	– intravenous

occurs as a superinfection of the pleural effusion [4].

The bacterial superinfection of SARS-CoV-2 is more common than in other respiratory viral syndromes and it may be a determining factor in the disease evolution. According to different studies around the world, its prevalence ranges between 1% and 50% and leads to prolonged hospitalization, severe clinical picture, admission to the intensive care unit, mechanical ventilation, and other complications [5]. Excessive use of antibiotics in the treatment of COVID-19 hospitalized patients may increase the risk of nosocomial infections caused by multidrug-resistant bacteria.

We are presenting patients with pleural complications of COVID-19 pneumonia, pneumothorax and empyema with isolated Acinetobacter spp.

Case 1

A 62-year-old female with a history of hypertension, unvaccinated to SARS-CoV-2, was admitted to the Department of Infection Diseases, COVID department, in the General Hospital of Novi Pazar, Serbia, complaining of worsening dyspnea, fever, headache, malaise, and cough. The symptoms began about 10 days before admission when she underwent rapid antigen and reverse transcription polymerase chain reaction (RT-PCR) nasopharyngeal swab testing and was diagnosed with the novel COVID-19. The worsening of breathing with SpO_2 of 60% required hospitalization. Initial chest radiography showed bilateral pneumonia **(Figure 1)**.

The initial laboratory tests showed the following: C-reactive protein 99.8 mg/L, Interleukin 6 56.9 pg/ml, procalcitonin 0.09 μg/L, Lactate dehydrogenase 897 IU/L, Fe 4.3 μmol/L, Ferritin 720.44 ng/ml, Red Blood Cell count 4.1 x 10^{12}/L, White Blood Cell count 5.5 x 10^9/L, Platelets count 319 x 10^9/L, Hemoglobin 127 g/L, Hematocrit 0.37U/L, D dimer 2 mg/L.

The initial treatment included antibiotics (ceftriaxone, azithromycin), analgesics, proton pump inhibitors, corticosteroids, and other supportive therapy. Oxygen saturation was 95% at a rate of 15 l/min O_2 on nasal cannula. Due to the worsening of the respiratory condition, on day 6 of hospitalization, the patient was transferred to high-flow nasal oxygen (HFNO) therapy (fraction of inspired oxygen 100%, Flow 60 l/min) for the next 7 days. During the rest of hospital stay, she was on oxygen support, through a nasal mask up to 20 l/min with SpO_2 up to 94%. After a month of hospitalization, still oxygen-dependent, the patient presented with a severe pain in the right hemithorax. Chest X-ray and computed tomography (CT) showed a right pneumothorax **(Figure 2)**.

After a month from the initial positive test for SARS-CoV-2, according to the protocol, the patient was no longer considered infectious and the rapid antigen test for SARS-CoV-2 was negative, the patient was transferred to the Department of Surgery of our hospital, for further treatment. For the right pneumothorax treatment, Fr28 chest tube was inserted. After this intervention, lung re-expansion occurred **(Figure 3)**. Throughout the hospitalization, the patient required oxygen support up to 10 l with saturation up to 94%. On the repeated RT-PCR nasopharyngeal swab for SARS-CoV-2, the patient was still positive, after 35 days of hospitalization. Ten days after drainage, an attempt was made to remove the chest tube; it

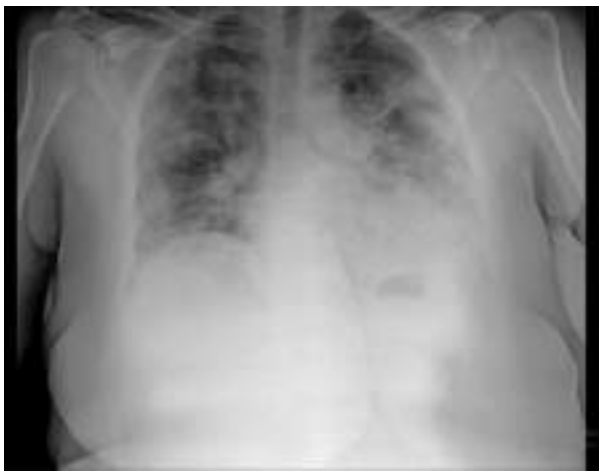

Figure 1. Multiple bilateral and diffuse confluent areas with predominantly peripheral localization indicating an advanced process of infectious etiology
Slika 1. *Bilateralne i difuzne višestruke konfluentne mrljaste senke pretežno periferne lokalizacije unutar uznapredovalog procesa infektivne etiologije*

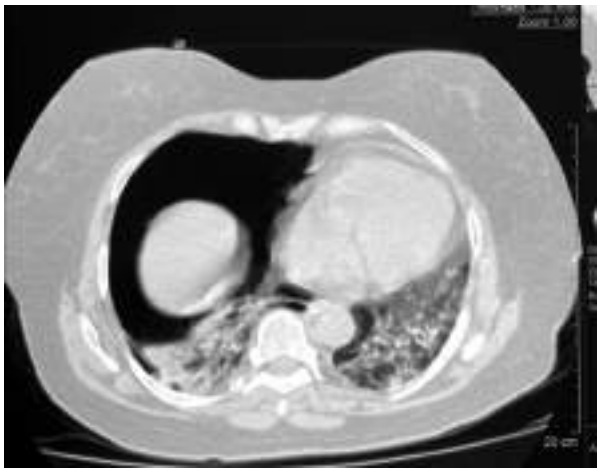

Figure 2. Right pneumothorax on chest CT after one month of hospitalization
Slika 2. *Desni pneumotoraks na snimku kompjuterizovane tomografije grudnog koša, nakon mesec dana hospitalizacije*

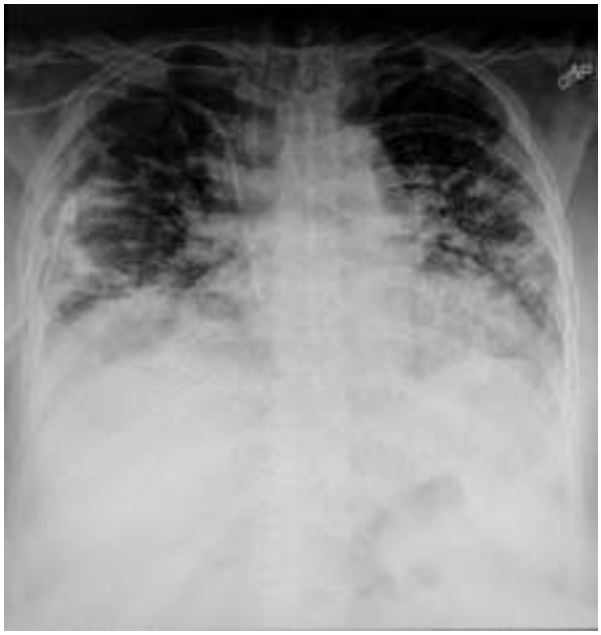

Figure 3. After chest drainage - pulmonary re-expansion
Slika 3. *Reekspanzija pluća nakon drenaže grudnog koša*

was not tolerated well, the saturation decreased and subcutaneous emphysema appeared, so the patient underwent redrainage. About 200 ml of liquid content was evacuated daily through the chest tube indicating the development of empyema. The initial swab was sterile. Due to the increase of inflammatory parameters and worsening of the general condition, the patient was transferred to a tertiary health institution, Thoracic Surgery, for further treatment.

Conservative treatment was continued. A control swab of the chest tube contents revealed Acinetobacter spp. sensitive only to imipenem and tigecycline. Blood cultures were sterile. Due to the general condition of the patient and the findings on the lungs caused by COVID-19 infection, conservative therapy was continued. Antibiotic therapy, according to the antibiogram, and supportive therapy were also continued. The patient responded well to the therapy.

The chest tube was removed on day 35 after insertion, and the patient was discharged for home treatment after 65 days of hospital stay.

Case 2

A 61-year-old female patient was admitted to our center presenting with shortness of breath, weakness, malaise, cough, nausea, and vomiting. The symptoms began 7 days before admission to the COVID Department, but got worse in the last 3 days. She was treated at home with antibiotics (azithromycin 500 mg twice a day and ceftriaxone 1 g/12/h IV), dexamethasone, integrated procedural platform, and supportive therapy.

The patient underwent surgery and radiotherapy for uterine cancer 2 years ago; she was treated for hypertension and was unvaccinated to SARS-CoV-2. Rapid serological test for SARS-CoV-2 (IgM and IgG negative), rapid antigen, and RT-PCR nasopharyngeal swab

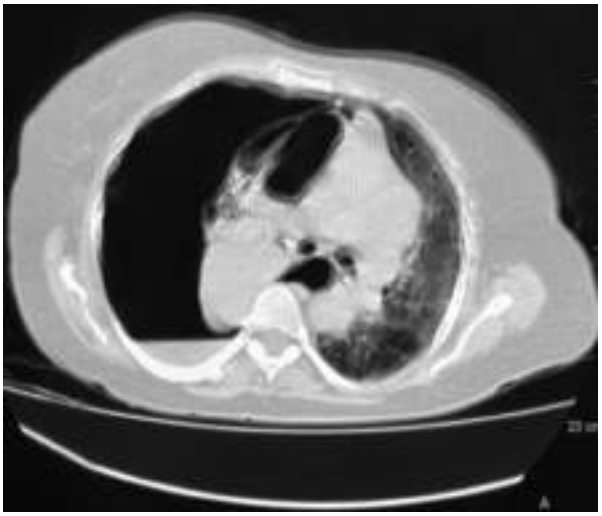

Figure 4. Right pneumothorax on a chest CT
Slika 4. *Desni pneumotoraks na snimku kompjuterizovane tomografije grudnog koša*

were positive. On admission, the patient presented with cyanosis, dyspnea and hypertension; she was afebrile with oxygen saturation of 52% and after application of oxygen 30 l/min the SpO_2 was 88%.

The initial laboratory test results were as follows: Interleukin-6 1120 pg/ml, C-reactive protein 230 mg/L, procalcitonin 0.08 µg/L, ferritin 697 ng/ml, Lactate dehydrogenase 1252 IU/L, Fe 3.8 µmol/L, Red Blood Cell 4.07 x 10^{12}/L, White Blood Cell 9.7 x 10^9/L, PLT 328 x 10^9/L, Hemoglobin 122 g/L, Hematocrit 0.35 U/L, D dimer 2.4 mg /L.

The chest X-ray showed a zone of incomplete consolidation in the lower field of the right lung and in the rest of the lung parenchyma there were multiple shadows of inflammatory etiology. During the first 13 days of hospitalization, the patient received HFNO (FiO_2 100%, flow 60 l/min). After that, she was on oxygen therapy through the nasal mask up to 15 – 20 l/min with SpO_2 up to 95%.

The patient was treated with conservative therapy: proton pump inhibitors (IPP), probiotics, fluids, antibiotics, corticosteroids, low-molecular-weight heparins (nadroparin calcium 0.6 mL/12 h), biological therapy - tocilizumab 8 mg/kg IV in two doses.

Mild regression of radiologically verified COVID-19 pneumonia occurred with the prescribed therapy. After 3 weeks of hospitalization, the patient presented with an increase in IL 6 (> 1000) and WBC (23.3) and right hydropneumothorax was established **(Figure 4)**. The patient was transferred to the Department of Surgery for further treatment. Chest tube Fr28 was inserted in the right hemithorax. After this intervention, lung re-expansion occurred **(Figure 5)**. The first three days after drainage, about 1600 ml of liquid content was extracted through the chest tube. Due to the worsening of the general condition and inflammatory parameters, the patient was transferred to a tertiary health institution, Thoracic Surgery Department for further treatment. A control swab of the chest tube

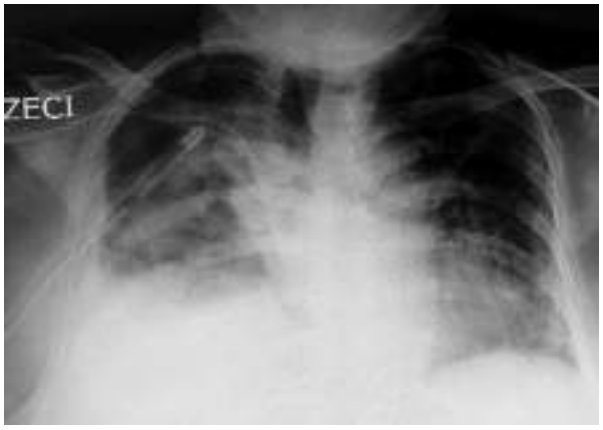

Figure 5. After chest drainage - pulmonary re-expansion
Slika 5. *Reekspanzija pluća nakon torakalne drenaže*

contents and blood cultures revealed Acinetobacter spp. sensitive only to tigecycline.

The patient did not respond well to the therapy and her condition was deteriorating. Apart from poor inflammatory parameters and general condition, she developed a septic infection that led to a lethal outcome on day 52 after the onset of COVID-19.

Discussion

According to the etiology, pneumothorax can be classified as spontaneous and traumatic. Secondary spontaneous pneumothorax occurs in patients with underlying lung disease [6].

Pneumothorax is an important complication of COVID-19 that is associated with increased mortality, morbidity, and health care costs [2, 7]. The data about the incidence of pneumothorax in COVID-19 patients are mostly obtained through published case reports of patients with COVID-19 with pneumothorax, and therefore it is unknown. Marciniak et al. found an incidence of 0.91% in COVID-19 patients. Similar results were reported by Chen et al. with 1% [8] and 2% of patients requiring intensive care unit admission in other studies [8–10]. Martinelli et al. also found that 1% of patients admitted with COVID-19 develop pneumothorax and this can occur without a pre-existing lung disease or mechanical ventilation [11]. It seems that it mostly affects males; patients who require noninvasive or invasive ventilatory support are at a higher risk [7].

The precise pathogenesis of pneumothorax in patients with COVID-19 has not been fully elucidated. According to the literature, parenchymal lung damage in COVID-19 with ischemic and inflammatory effects may increase the incidence of pneumothorax, such as surfactant changes, loss of extracellular matrix and basement membrane in COVID-19-infected lung tissue, or pulmonary cyst rupture. Coughing has also been associated with pneumothorax via the Macklin effect [12, 13].

Both of our patients were elderly females, nonsmokers, without previous lung disease, critically ill and both were on HFNO and prolonged oxygen therapy.

Empyema developing in COVID-19 pneumonia is rarely reported in the literature. Tessitore et al. reported that a strong inflammatory response causes reactive pleural effusion and empyema with bacterial superinfection [14]. This is confirmed by other authors (2 – 14). The COVID-19 infection may predispose to secondary bacterial infection which is associated with poor clinical outcomes, especially among critically ill patients. In contrast to other coronaviruses, SARS-CoV-2 has been associated with an increase in secondary bacterial infections. Several studies have reported that a variable percentage of COVID-19 patients (4 – 20%) have bacterial and/or fungal co-infection. In recent meta-analysis, bacterial co-infection was reported in 7% of hospitalized patients with COVID-19 and up to 14% in critically ill patients or those with secondary infection [15–17].

The empiric use of antibiotics in a great number of hospitalized patients with COVID-19 is reported in many studies. It is shown that the inflammatory markers, such as increased levels of procalcitonin and C-reactive protein, which are usually associated with bacterial infection, may appear without an existing bacterial co-infection in COVID-19 patients [17]. Fan et al. observed that lung microbiota of deceased patients with COVID-19 exhibited complex bacterial and fungal colonization by opportunistic species [18]. Excessive and uncritical use of antibiotics in the treatment of these patients, as well as long-term hospitalization, with or without mechanical ventilatory support, may lead to superinfection of nosocomial bacterial strains resistant to most antibiotics. In the study of Clansy et al., potential bacterial lung superinfections were evident at postmortem examination in 32% of persons who died of COVID-19. They also noted that 3.5% of patients had empyema, and lung superinfections were the cause of death in 3% of all patients with COVID-19 [19]. Yet, despite the increasing number of COVID-19 studies, the predisposition of COVID-19 patients to secondary infection is not fully understood [15]. Our data are in accordance with the literature data.

Acinetobacter spp. has been implicated in nosocomial infections of clinical importance in the elderly, infants, and immune-compromised patients. Acinetobacter spp. infections lead to high mortality and morbidity, prolonged hospital stay with high treatment costs.

Although most Acinetobacter species are nonpathogenic, they are an important reservoir of antibiotic resistance. Multidrug-resistant Acinetobacter is a major concern in hospitals in many parts of the world. Olu-Taivo et al. found 62% resistance to at least three or more antimicrobial agents [20]. This is in line with previous reports from Italy (54%) and the United States (72%) [21, 22]. Both of our patients were treated with antibiotics for a long

period of time and the isolated Acinetobacter was resistant to almost all antibiotics.

Conclusion

Pulmonary complications in hospitalized patients with coronavirus disease 2019 increase the mortality rate and the development of more severe clinical forms of the disease. Extensive and long-term use of antibiotics may increase the incidence of nosocomial superinfections. Further researches are needed to better understand this disease.

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Case report
Prikaz slučaja
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SYSTEMIC TREATMENT OF HEPATOCELLULAR CARCINOMA IN A PATIENT WITH HEMOPHILIA A – A CASE REPORT

SISTEMSKA TERAPIJA HEPATOCELULARNOG KARCINOMA KOD PACIJENTA SA HEMOFILIJOM A – PRIKAZ SLUČAJA

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Summary

Introduction. Hepatocellular carcinoma is a serious problem for patients with hemophilia. Hepatitis C virus infection is the most common comorbidity in adult patients with inherited bleeding disorders, including hemophilia. **Case Report.** This is a case report of a 65-year-old male patient with hemophilia A and hepatocellular carcinoma. Sorafenib treatment was initiated at a dose of 400 mg/day, after a 50% dose reduction. In order to prevent bleeding episodes, prophylactic doses of replacement plasma-derived factor VIII concentrate (40 U/kg of body weight three times a week) were introduced. Our patient received a total of ten cycles of sorafenib therapy, in good general condition, without bleeding episodes. **Conclusion.** Differential chemotherapy is not contraindicated in patients with inherited bleeding disorders, provided that adequate hemostasis is achieved. In such cases, a multidisciplinary approach is necessary for the management of hemophilia during systemic cancer treatment.

Key words: Hemophilia A; Carcinoma, Hepatocellular; Sorafenib; Antineoplastic Agents; Factor VIII; Hemorrhage; Hemostasis; Diagnosis; Treatment Outcome; Drug-Related Side Effects and Adverse Reactions

Sažetak

Uvod. Hepatocelularni karcinom predstavlja ozbiljan problem za pacijente sa hemofilijom. Infekcija virusom hepatitisa C je najčešći komorbiditet kod odraslih pacijenata sa naslednim poremećajima krvarenja, uključujući hemofiliju. **Prikaz slučaja.** Predstavićemo slučaj iz naše ustanove, 65-godišnjeg pacijenta koji boluje od hemofilije A i hepatocelularnog karcinoma. Lečenje sorafenibom je započeto smanjenjem doze za 50% od 400 mg/dan. Da bi se sprečile epizode krvarenja, uključene su profilaktičke doze supstitucione terapije koncentratom faktora VIII iz plazme (40 U/kg telesne težine tri puta nedeljno). Naš pacijent je primio ukupno deset ciklusa sorafeniba, u dobrom opštem stanju, bez epizoda krvarenja. **Zaključak.** Diferentna onkološka terapija može da se sprovodi kod pacijenata sa nasledim poremećajima krvarenja, pod uslovom adekvatne korekcije hemostaze. U ovakvim slučajevima neophodan je multidisciplinarni pristup za lečenje hemofilije tokom sistemskog lečenja karcinoma.

Ključne reči: hemofilija A; hepatocelularni karcinom; sorafenib; antineoplastični lekovi; faktor koagulacije VIII; krvarenje; hemostaza; dijagnoza; ishod lečenja; nuspojave i neželjene reakcije izazvane lekovima

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men, the ninth in women, and the second most common cause of cancer-related death worldwide [1]. Up to 80% of HCC cases are associated with two viruses alone i.e., hepatitis C virus (HCV) and hepatitis B virus (HBV). Hepatitis C virus infection is the most common comorbidity in adult patients with inherited bleeding disorders, including hemophilia [2, 3]. According to Darby et al., in patients with hemophilia, the mortality is 16.7 times higher than in the general population for liver disease, and 5.6 times higher for liver cancer [4]. Therefore, HCC is a critical problem for hemophilia patients. The treatment of HCC depends on the stage of the disease. It includes surgical tumor resection, liver transplantation, chemoembolization, as well as systemic administration of sorafenib, a multikinase inhibitor. In the available literature, there are few reports on patients with hemophilia and HCC treated with sorafenib. We present a case from our clinical practice.

Case Report

A 65-year-old male patient with hemophilia A was admitted to the Regional Center for tooth extraction. As part of the preoperative preparation, impairment of the liver function was observed. Additional serological tests were performed and HCV was diagnosed. After assessment by an infectologist, a regular follow up was indicated. Furthermore, abdominal computed tomography was performed **(Figure 1)** and tumor lesions in the segment (S)5 and S6 of the liver, ranging in size from 60

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Abbreviations

HCC – hepatocellular carcinoma
HCV – hepatitis C virus
S – segment
MRI – magnetic resonance imaging

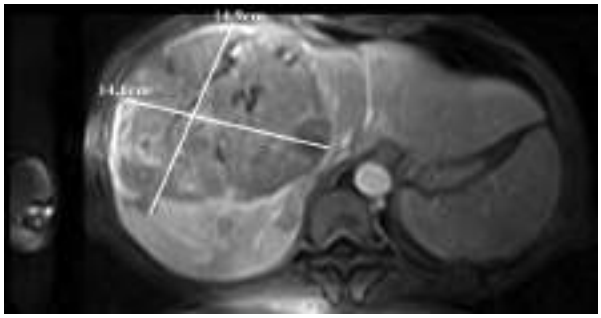

Figure 1. Abdominal MRI at the time of HCC diagnosis (August 2019)
Slika 1. *Magnetna rezonancija abdomena u momentu postavljanja dijagnoze (avgust 2019.)*

to150 mm, were found. Tumor marker alpha-fetoprotein (AFP) was elevated (over 100 ng/ml).

Esophagogastroduodenoscopy and total colonoscopy were performed and showed no pathological findings. Abdominal magnetic resonance imaging (MRI) was performed and expansive liver lesion was found in S8 (131 x 145 x 137 mm in size), with typical HCC characteristics. Also, there was a suspicious involvement of the peritoneum, infiltration of the diaphragm, compression and probably infiltration of the main liver vessels. Retroperitoneal lymphadenomegaly and signs of portal hypertension were also reported. The functional liver status, according to Child-Pugh score (class A) was 5. According to the Barcelona Clinic Liver Cancer Criteria, the patient was stage C. The case was presented to a multidisciplinary team of our institute, where it was decided to continue the treatment with tyrosine kinase inhibitor - sorafenib. Sorafenib treatment was initiated at a dose of 400 mg/day, after a 50% dose reduction. In order to prevent bleeding episodes, prophylactic doses of replacement plasma-derived factor VIII concentrate (40 U/kg of body weight three times a week) were introduced, according to guidelines for managing hemophilia patients that were previously established [5]. Our patient received ten cycles of sorafenib therapy and he was in a good general condition, without bleeding episodes. After every two cycles a complete restaging was performed **(Figure 2)** and MRI of the abdomen showed a stable disease. The functional liver status, according to the Child-Pugh score, was 5. After a total of ten cycles, radiological and clinical progression of the disease was noted.

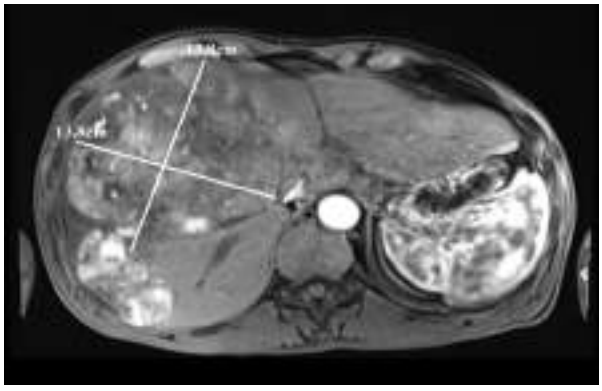

Figure 2. Abdominal MRI after sixth cycles of sorafenib therapy (June 2020)
Slika 2. *Magnetna rezonancija abdomena nakon šest ciklsa sorafeniba (jun 2020.)*

Discussion

Sorafenib is a multikinase inhibitor which blocks the growth of tumor cells by inhibition of several pathways which interfere with angiogenesis. It has been shown to antagonize the angiogenic effect of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) on their receptors VEGFR2 and PDGFR, respectively. Anti-angiogenic drugs show a great spectrum of both thrombotic and hemorrhagic complications. The most common adverse reactions are diarrhea, fatigue, alopecia, infection, hand-foot skin reaction, and rash. Among the most important serious adverse reactions is hemorrhage with an incidence of 2 – 3% in treated patients, ranging from frequent and mild to rare severe hemorrhages [6, 7]. To our knowledge, only one case report discussed the use of sorafenib in the treatment of HCC in patients with hemophilia [8]. In that case report the patient received only two cycles of sorafenib.

Our experience suggests that hemostasis correction is critical in patients receiving sorafenib, to prevent bleeding complications associated with the use of this drug. Prophylactic treatment with factor VIII concentrates is associated with a better long-term outcome when compared to on-demand treatment.

Conclusion

Differential chemotherapy is not contraindicated in patients with inherited bleeding disorders, provided that adequate hemostasis is achieved. In such cases, a multidisciplinary approach is necessary for the management of hemophilia during systemic cancer treatment.

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THE EFFECTS OF VITAMIN B12 DEFICIENCY

POSLEDICE DEFICITA VITAMINA B12

Marko KOPRIVICA[1], Jelena BJELANOVIĆ[1, 2] and Radmila VELICKI[1, 2]

Summary
Vitamin B12 is one of the most important B vitamins. This vitamin has an important role in cellular metabolism and is also associated with folate and vitamin B6 metabolism. Vitamin B12 deficiency occurs as a result of some diseases, the use of certain medications, or inadequate nutrition. It primarily affects the elderly and women, but is also common among the pediatric population. The B12 deficiency mostly affects the functions of the nervous and hematopoietic systems but it can also affect the skin, heart, bones, and eyes. The treatment of vitamin B12 deficiency includes oral or intramuscular vitamin B12 supplementation according to different treatment regimens.
Key words: Vitamin B 12 Deficiency; Vitamin B 12; Dietary Supplements; Transcobalamins; Risk Factors; Nervous System Diseases; Hematologic Diseases; Metabolic Diseases; Biological Availability; Anemia, Megaloblastic

Sažetak
Vitamin B12 jedan je od najvažnijih vitamina B grupe. Ovaj vitamin ima značaju ulogu u celularnom metabolizmu, a povezan je i sa metabolizmom folata i vitamina B6. Deficit vitamina B12 nastaje kao posledica određenih oboljenja, primene lekova ili usled neadekvatne ishrane. Prvenstveno se javlja kod starijih osoba i žena, ali je čest i među pedijatrijskom populacijom. Posledice nedovoljnih koncentracija najviše se ispoljavaju na nervnom i hematopoetskom sistemu, ali se mogu javiti i na koži, srcu, kostima i oku. Lečenje deficita zahteva nadoknadu vitamina B12 oralnim ili intramuskularnim putem po različitim šemama.
Ključne reči: deficit vitamina B12; vitamin B12; dijetetski suplementi; transkobalamini; faktori rizika; oboljenja nervnog sistema; hematološka oboljenja; metabolička oboljenja; biološka raspoloživost; megaloblastna anemija

The structure and synthesis of vitamin B12

Vitamin B12 (cobalamin) is one of the most important B vitamins [1]. It is the largest and most structurally complex vitamin in the human body. It has a corrin ring shaped nucleus similar to those of hemoglobin and chlorophyll. The central metal ion in vitamin B12 is cobalt, which binds to various chemical groups, including cyano, hydroxy, methyl, and 5'-deoxyadenosyl. The latter two are active forms of vitamin B12 used for specific catalyzing enzymatic reactions in the human body [2]. It affects two enzymes, methionine synthase and methylmalonyl-CoA mutase [3]. It consists of a corrin nucleus to which a pendant group and a nucleotide residue are bonded. This vitamin plays a role in catalyzing enzymatic reactions essential for proper functioning of the nervous and hematopoietic systems [1]. The recommended daily dose of vitamin B12 for an adult is 2.4 mg [4, 5]. Children, the elderly, pregnant women, and lactating mothers have increased requirements for cobalamin. These vulnerable groups are at a higher risk of developing vitamin B12 deficiency due to both their reduced intake and increased requirements for cobalamin [1]. Vitamin B12 plays a significant role in cellular metabolism and is closely related with folate and vitamin B6 metabolism [6]. Vitamin B12 is a crystal compound, red in color, with a molecular weight of 1.4 kDa. The base of the molecule is its corrin nucleus, because of which this group of molecules is called corrinoids. The corrin nucleus is composed of 4 interconnected reduced pyrrole rings in the centre of which is cobalt connected by the hydrogen links with other parts of the molecule. The side group of molecules comprises phosphoribosyl 5,6-dimethylbenzimidazole, whose nitrogen molecule is connected with cobalt. Nucleotide residue producing cobalamin derivatives may also be part of the basic molecule [7]. The highest percentage of vitamin B12 in the human body comes from food, while the rest is synthesized by bacteria in the intestinal tract [8]. There are two basic ways of synthesis differentiated by the time of cobalt integration into the corrin nucleus [8]. Cobalt integration represents the first step requering oxygen in the aerobic path. In contrast, in the anaerobic path, insertion comes in later phases, and presence of oxygen is not mandatory. Synthesis can be performed as de novo, when a complete

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Abbreviations
DNA – deoxyribonucleic acid

molecule is synthesized by bacteria from δ-aminolevulinic acid or by salvage path when corrin ring is inserted from the exogenous environments [8].

Metabolism and function of vitamin B12

The absorption of vitamin B12 begins in the mouth. After binding with the R protein, it is transported from the stomach to the distal ileum, where it is absorbed into erythrocytes. There, it is linked with transcobalamin II protein, and is released into the circulation and distributed into all body parts performing its function [9]. Vitamin B12 is mostly stored in the liver that contains between 2 – 3 mg of this vitamin. The excretion is done through urine and bile when repeated vitamin intake occurs in the enterohepatic circulation [7].

In addition to insufficient vitamin intake, B12 deficiency may be caused by a number of diseases and conditions. Among these, cobalamin deficiency is most commonly caused by atrophic gastritis (associated with Helicobacter pylori infection), pernicious anemia (autoimmune destruction of gastric parietal cells and intrinsic factor deficiency), distal ileum diseases (intestinal resection, inflammatory disease, Whipple's disease, ileocecal tuberculosis), stomach resection (partial or complete), infections (colonization of the small intestine by parasites and bacteria), congenital syndromes and genetic disorders (deficiency or functional impairment of transcobalamin, cobalamin gene mutations) [10]. Many epidemiological studies and animal models have shown a link between vitamin B12 and various components of metabolic syndrome. A high prevalence of low B12 levels has been shown in European (27%) and South Indian (32%) patients with type 2 diabetes. A longitudinal prospective study in pregnant women showed that low B12 status may independently predict the development of type 2 diabetes five years after delivery. Also, children born to mothers with low B12 levels may have excess fat accumulation [10].

Vegans and vegetarians are at higher risk of developing B12 deficiency due to the foods they consume in their daily diet not being rich in vitamin B12. Therefore, vegetarians who consume no foods of animal origin are considered a risk group for vitamin B12 deficiency [11, 12]. Cobalamin deficiency is significantly more common in the elderly and women [13]. The elderly persons are at an increased risk of developing vitamin deficiencies due to their reduced dietary intake caused by their reduced physical capacity (difficulty preparing food themselves, psychological factors such as depression), and the development of certain diseases. Vitamin B12 deficiency may also be caused by use of medications (proton pump inhibitors, metformin, antiepileptic drugs, colchicine, and nitric oxide) [14, 15]. Vitamin B12 deficiency is also commonly observed in women, especially during pregnancy and lactation, since the cobalamin requirements are increased in these periods [13].

This type of deficiency affects almost all organs and organ systems, particularly the nervous and hematopoietic systems [16, 17]. In addition, reduced cobalamin concentrations lead to the demyelination of the central and peripheral nerve fibers, which is also considered the leading cause of pathological changes in the nervous system. These changes primarily affect the sensory nerves that participate in general sensibility (touch, vibration, position), but motor neurons may be affected as well.

Vitamin B12 deficiency in early childhood is a significant cause of neurodevelopmental delay [18]. Intrauterine deficiency leads to the development of neural tube defects (spina bifida, anencephaly, encephalocele), while in adults, it manifests as cerebrovascular disease (occlusion of coronary and cerebral arteries), cognitive dysfunction, neuropsychiatric disease (hypomania, depression), spinal cord degeneration (paresthesia, loss of sense of position and vibration), peripheral neuropathy (paresthesia, stiffness), or optical neuropathy (visual acuity loss, visual field loss) [16].

Vitamin B12 deficiency can increase homocysteine levels, which is considered a risk factor for ischemic stroke [19, 20]. Certain studies show that vitamin B12 may play a significant role in lowering homocysteine levels, thus preventing stroke. In case studies of forty-year-olds with progressive sensory and motor impairments from the lower extremities extending into the middle thoracic region, the diagnosis of subacute spinal cord degeneration, which occurred due to vitamin B12 deficiency, was confirmed by laboratory tests and magnetic resonance imaging [21]. In content of the previous claim is also a case study of a 37-year-old woman with ataxia, lower extremity proprioception loss, dorsal spine demyelination, and other laboratory findings confirming nitric oxide abuse. Nitric oxide irreversibly inactivates vitamin B12, causing dorsal spine demyelination, which is clinically indistinguishable from that caused by vitamin B12 deficiency [22].

As for the hematopoietic system, cobalamin deficiency leads to the development of megaloblastic anemia [23, 24]. This disease is characterized by dysfunctional erythrocyte structure and function, manifested through insufficient hemoglobin synthesis and transport of oxygen to target tissues [24]. Also, one case study shows a 17-year-old male diagnosed with pseudothrombotic microangiopathy caused by vitamin B12 deficiency [25]. Insufficient hemoglobin synthesis is a result of inappropriate thymidylate synthase and decreased thymine synthesis, and for this reason, uracil is incorporated into the deoxyribonucleic acid (DNA) strand instead of thymidine during synthesis. Since uracil is most commonly incorporated into both DNA strands at positions close to one another, the molecule reparation results in double-stranded breakage and DNA damage. Such changes to the DNA lead to slow maturation of nucleic acids and a decrease in cell division, resulting in pancytopenia. Cells that enter the division have a nucleus that is immature compared to the cytoplasm, and the final product of the division is a large cell with an immature, segmented nucleus. These changes are particularly pronounced in red blood

cell precursors, causing macrocytic anemia [24]. Pernicious anemia, if left untreated, can be fatal [26].

The primary role of red blood cells is to transport oxygen. When the number of erythrocytes is inadequate, organs do not receive enough oxygen. This blood disorder is known as anemia. There are different types of anemia; megaloblastic anemia is characterized by erythrocytes that are larger than normal and cannot get out of the bone marrow to enter the bloodstream and deliver oxygen. The molecular basis of this cytomorphological aberration remains unknown. This clinical condition indicates that DNA synthesis is altered due to the lack of vitamin B12 needed for erythrocyte production and maturation. In particular, the cytoplasm overgrows the nucleus, causing their accumulation in the bone marrow (megaloblastosis) and macrocytosis in the peripheral blood. A characteristic feature of megaloblastic anemia is the mean corpuscular volume > 100 fL, which is often associated with a decrease in the number of mature blood cells (cytopenia) [27]. A case study clearly showed the occurrence of hypersegmented neutrophils in the blood and megaloblastic erythrocytes in the bone marrow; this phenomenon was due to vitamin B12 deficiency [28].

Apart from the nervous and hematopoietic systems, vitamin B12 deficiency also affects the development of cardiovascular disease and osteoporosis [29]. In addition, reduced cobalamin concentration leads to the development of skin hyperpigmentation. Changes may be generalized, but occur primarily on the flexor areas, palms, soles, oral cavity, and the back [30]. Cobalamin deficiency also affects the development of general weakness and may cause macular degeneration [31].

Vitamin B12 deficiency is diagnosed based on medical history and additional tests, including complete blood count with reticulocyte count (flow cytometry, peripheral blood smear), biochemical analyses (bilirubin and lactate dehydrogenase), specific tests (determination of cobalamin, homocysteine, transcobalamin II, and methylmalonic acid levels in the serum and urine), bone marrow biopsy, electromyography and magnetic resonance imaging (in case of suspected neurological complications) [32].

Daily requirements and bioavailability of vitamin B12

Vitamin B12 daily requirements primarily depend on the person's age. The recommended daily intake is the average daily intake that satisfies vitamin B12 requirements in 97 – 98% of healthy individuals. Infancy, childhood, and adolescence are periods characterized by rapid growth and increased needs for vitamin B12. In the first 12 months of life, the concentration of vitamin B12 is significantly reduced in breastfed infants. After 6 months and with gradual introduction of milk into the diet, vitamin B12 concentration increases to a maximum between the age of 3 and 7 years. Along with further growth, vitamin B12 needs increase up to the age of 14 years. After this period, the required dose of the vitamin is equal in adolescent and adult population. During pregnancy and lactation, women need higher concentrations than usual [33]. The bioavailability of vitamin B12 in fortified foods is very high. Preliminary results of an unpublished Australian study showed that the use of fortified foods gave significantly better results than intramuscular application of vitamin B12 or use of dietary supplements [34]. Dietary supplements are preparations added to food as concentrated sources of vitamins, minerals, or other substances playing a nutritional and physiological role in the human body. They are recommended when the diet does not provide the recommended daily intake. Vitamin B12 is available as a dietary supplement and a medication allowing easy application. Although sublingual application is recommended as a better option, there is no evidence supporting its efficiency over other preparations. The analysis of dietary supplements points out that smaller vitamin doses at more frequent intervals are significantly more efficient. It has been illustrated that application of 0.1 and 0.5 mg led to 52% to 97% of absorption. Application of 1 – 5 mg reduced absorption to 56 – 28%, and application of even higher doses (10 – 50 mg) led to a decrease in absorption to 3 – 16% [35].

Thermal processing causes almost 33% vitamin B12 loss in meat [36]. Analysis of 100 g of mutton using radioactive vitamin B12 showed its bioavailability between 56% and 77% [37], while in chicken, it was 65% [38]. Nearly 65% of vitamin B12 is absorbed from cow milk. Significant concentrations of vitamin B12 are lost by milk processing. Pasteurization of 2 – 5 minutes results in 30% loss, while 30 minutes of boiling leads to a loss of 50% [39]. Cooling of pasteurized milk in home conditions does not lead to vitamin B12 reduction [40]. Fermented milk stored at 48°C for 14 days leads to cobalamin concentration reduction, but 20 – 60% of vitamins already present in the milk will be preserved in the final fermentation product. The highest quantity of vitamin B12 is stored in the egg yolk. Bioavailability is lowest in scrambled eggs with 3.7% and the highest in fried egg with 9.2% [40, 41]. Food processing causes 2.3 – 14.8% loss [42, 43]. The bioavailability of vitamin B12 in 100 g of fish is about 38% [44]. Some researches show that tea is an excellent means of enriching the diet with folate and vitamin B12. In India, such a project has the potential to help eliminate certain hematological and neurological complications resulting from inadequate nutrition or poor absorption of folate and vitamin B12 [45].

Treatment of vitamin B12 deficiency

Vitamin B12 deficiency is most commonly caused by inadequate dietary intake [46]. In patients without neurological complications, the treatment begins with intramuscular administration of hydroxocobalamin at a dose of 1000 μg three times a week for two weeks. In patients with neurological symptoms, 1000 mg of vitamin B12 is administered every other day until symptoms improve, but no longer than three months [47]. The treatment effect should be visible in the bloodstream 7 to 10 days after initiating the therapy. Oral administration of high doses of vitamin B12 (1 do 2 mg daily) is as effective as intramuscular administra-

tion for treating anemia and neurological symptoms. Intramuscular therapy leads to faster improvement of symptoms in patients with severe deficiency and severe neurological symptoms [48]. The suggested oral dose of vitamin B12 is 1 mg daily for one month, followed by a maintenance dose of 125 to 250 mg for patients with nutritional insufficiency and 1 mg daily for those with pernicious anemia.

Maintenance therapy involves intramuscular administration of 1000 μg of vitamin B12 every three months or every two months if patients have neurological symptoms [47]. In infants, 250 – 1000 mg is administered intramuscularly on daily basis, then once a week, and then until the stabilization of health issues. Once adequate doses have been reached, supplementation is continued via oral doses (1 – 2 mg). Apart from the infant, the mother is also subjected to treatment to regulate vitamin levels in the milk [24].

A balanced and varied diet is the primary way to prevent vitamin B12 deficiency. Supplementation is necessary in people with insufficient intake of cobalamin or those with increased requirements for this vitamin [24, 47]. Reduced vitamin B12 concentration affects nearly all organ systems, particularly the nervous and hematopoietic systems, manifesting numerous symptoms [17]. Vitamin B12 deficiency may also occur during pregnancy, with adverse outcomes in mothers and infants [48]. The deficiency should be treated by restoring adequate vitamin B12 concentration for a period long enough to eliminate health issues it has caused and prevent the development of further complications [24, 47].

Conclusion

Vitamin B12 is one of the most important vitamins in the human body. Its functions mirror in catalysis of enzymatic reactions that are significant phases in blood cell formation and synthesis of molecules that build the nerve sheath. Maintenance of vitamin B12 levels during our entire life is the key factor for optimal health. Since vitamin B12 is primarily found in animal food products, a regular and diverse diet is mandatory for vitamin maintenance. Although the significance of vitamin B12 in our diet has been recognized almost one century ago, permanent education about its importance in everyday diet is necessary. Special attention should be paid to individuals with reduced intake of this vitamin, pregnant women and breastfeeding mothers, because prevention of B12 deficiency in mothers will prevent it in children as well.

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Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

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4. Literatura

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

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

∗ Bez autora

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

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

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

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

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

∗ Disertacija

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

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

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A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

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

∗ *No author given*

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

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

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

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

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

∗ *A dissertation and theses*

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

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.