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EVALUACIJA VERTEBRALNE STABILNOSTI NAKON POVREDA VRATNE KIČME

EVALUATION OF VERTEBRAL STABILITY AFTER CERVICAL INJURIES

Aleksandar MILIČIĆ

Sažetak
U radu je prikazan mogući algoritam za dijagnostiku i tretman nestabilnih povreda vratne kičme. On opisuje i rezultate implementacije različitih mehanizama povređivanja sa stvaranjem specifičnih posttraumatskih stanja i putokaz je u kom pravcu treba krenuti dalje. Pritom je posebno značajno prepoznavanje stabilnih i nestabilnih delova vratne kičme sa preporukom za određeni, specifični, pristup svakom od njih.
Ključne reči: Vratni pršljenovi + povrede; Dijagnoza; Povrede kičme; Algoritmi; Nestabilnost zglobova; Pozicioniranje pacijenta; Vodič

Summary
This study is the proposal of a possible algorithm for the diagnosis and treatment of unstable cervical spine injuries. It also describes the results of implementation of different mechanisms of injury with the formation of specific posttraumatic conditions; it indicates in which direction to move on. Thereby, it is of particular importance to recognize stable and unstable entity of cervical spine with a recommendation for a specific access to any of them.
Key words: Cervical Vertebrae + injuries; Diagnosis; Spinal Injuries; Algorithms; Joint Instability; Patient Positioning; Guideline

Uvod

Dijagnoza povrede vratne kičme često je prikrivena i teška za pepoznavanje. Samim tim povređene osobe su pod povećanim rizikom od nastanka različitih, manjih ili većih komplikacija, uključivši i samu tetraplegiju [1−5].

Cilj rada je da prikaže vlastita iskustva sa nestabilnim povredama vratne kičme i da predstavi jedan od mogućih protokola za njihovo efikasnije rešavanje.

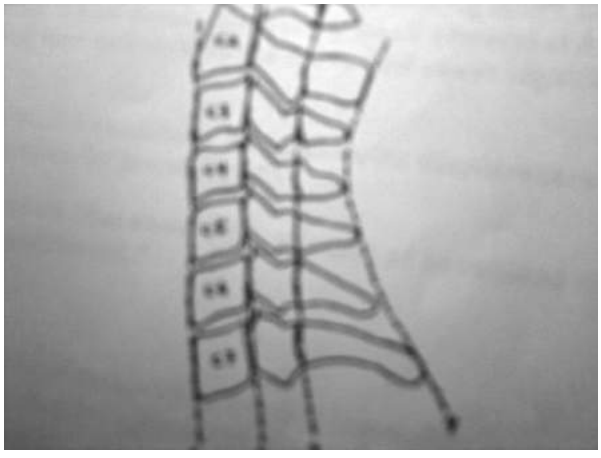
Materijal i metode

Za potrebe studije korišćeni su kompletirani podaci iz medicinske dokumentacije 78 pacijenata sa povredom vratne kičme koji su lečeni u Kliničkom centru Vojvodine u petogodišnjem periodu (2006–2010. godine). Najviše je bilo osoba muškog pola prosečne starosti 42 godine (18−56 godina). Uzroci povređivanja bili su automobilski akcidenti kod 32 pacijenta, skok ili pad sa visine (26 pacijenata), sportski akcidenti (14) i drugi redi uzroci (6). Operativni zahvat stabilizacije kičme po Roy-Camilleu preduzet je kod 50 pacijenta (64%) i konzerativno lečenje halo trakcijom i /ili plastičnim okovratnikom kod 28 (36%).

Kod svih je izvršen detaljan klinički pregled, a predomantni metod analize dobijenih podataka bila je evaluacija rezultata dobijenih radiografskom studijom prema kriterijumima kliničke stabilnosti cervikalne kičme po Whiteu i saradnicima iz 1990. godine [6].

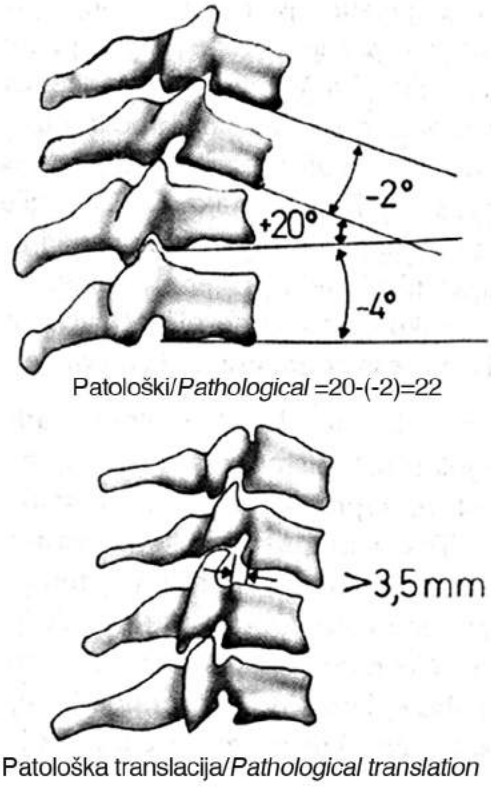
Rezultati

Neprepoznavanje traume, sa zakašnjenjem u dijagnozi lezije vratne kičme, zabeleženo je kod



Slika 1. Pomoćne linije za dijagnostiku
Fig. 1. *Adjuvant lines for diagnostics*

Adresa autora: Prof. dr Aleksandar Miličić, Klinika za ortopedsku hirurgiju i traumatologiju, 21000 Novi Sad, Hajduk Veljkova 1-7



Slika 2. Znaci nestabilnosti vratne kičme
Fig. 2. *Signs of unstable cervical spine*

28 pacijenata. Uzroci previda najčešće su bili radiogrami koji tehnički nisu uspeli ili nisu pravilno interpretirani (15 snimaka). Kod preostalih inicijalno neprepoznatih pacijenata radilo se o klasičnim previdima, bez postavljene bilo kakve sumnje da je prisutna spinalna lezija.

Na kraju lečenja pacijenata iz serije hospitalizovanih i operisanih, 50 je imalo stabilnu kičmu bez znakova hipermobilnosti, a u dva slučaja registrovan je prekomerni bolni kifotični deformitet vrata. Nasuprot tome, hronična nestabilnost je nađena čak kod 12 pacijenata (43%) iz konzervativno lečene serije i to kod 8 povređenih koji su inicijalno bili bez svesti, 2 sa tetraplegijom i 2 sa različitim drugim manjim povredama. Kliničko-radiološki nalaz na kraju lečenja pokazao je značajno poboljšanje u obe serije, pa se prisustvo neurološkog deficita svelo na 2 slučaja cervikalne mijelopatije.

Diskusija

Iako postoji napredak u dijagnostici spinalnih povreda, pitanje previda i zakašnjenja u postavljanju dijagnoze predstavlja veliki, još nerešeni problem, koji može da ostavi teške posledice. Da bi se taj problem umanjio i broj previđenih slučajeva sa povredom vratne kičme redukovao na najmanju moguću meru, pokazalo se da je potrebno držati se nekih osnovnih postulata. Pravilo je da kod posttraumatskih stanja, na prisustvo preloma vratne kičme treba sumnjati sve dok se detaljnim ispitivanjima takva dijagnoza ne prihvati ili ne odbaci. Takođe, neophodno je držati se pravila da svaku politraumu, teške udružene i kombinovane povrede, besvesna stanja i povrede koje u svojoj osnovi prate klasične mehanizme povređivanja kičme (pad sa visine, skokovi u vodu i sl.) moraju pobuditi sumnju na mogućnost preloma vratne kičme i njenu nestabilnost [7–11].

Međutim, praksa je pokazala da ovakav mehanistički pristup nije uvek dovoljan da se postavi precizna dijagnoza prikrivene vertebralne povrede. Kliničke i eksperimentalne studije raznih autora pokazale su veliku učestalost hronične posttraumatske nestabilnosti sa rasponom pojavljivanja od 4,5% do 33%, što pokazuju i naši rezultati (28%). Sve ovo govori da se radi o teškim stanjima koja sama po sebi predstavljaju nerešen dijagnostički problem. Zbog svega navedenog, ogroman je značaj korišćenja kombinovanih kliničkih i radiografskih − kompjuterizovana tomografija i magnetna rezonancija i, posebno, dinamičkih studija koje adekvatno primenjene vode do definitivno visokog stepena (preko 80%) prepoznavanja specifične vertebralne traume [12,13].

U spinalnoj dijagnostici izuzetno je značajno razmatranje i pravilna interpretcija linearnih radiografskih merenja. Strukturalni integritet lateralnih radiografija cervikalne kičme najbolje se vidi ucrtavanjem 4 lučno konturisane isprekidane linije konveksne napred (**Slika 1**), koje se povlače preko prednjih ivica tela pršljenova, preko zadnje strane trupa, na bazi lamina i preko vrhova spinoznih nastavaka. Najmanji prekid u kontinuitetu (znak bajoneta) bilo koje od tih linija indikuje postojanje povrede mekih tkiva i potencijalno prisustvo kliničke nestabilnosti. Ako akutni horizontalni deplasman, mereno na neutralnim, lateralnim ili fleksiono ekstenzionim profilnim radiografijama prelazi 3,5, mm viđeno na standardnim radiografijama kod neposredno povređenog pacijenta, tu veličinu translacije treba razmotriti kao abnormalan pokret i indikovati prisustvo nestabilnosti. Ako je tu lokalna angulacije veća od 11 stepeni u odnosu na angulaciju bilo koje susedne vertebre, takođe se radi o nestabilnosti vratne kičme. Dopunski elementi koji pomažu u preciziranju dijagnoze odnose se na suženje dijametra kičmenog kanala ispod 12 mm, povećanje prostora između prednjeg luka atlasa i densa aksisa preko 2-3 mm, kao i povećanje prevertebralne senke mekih tkiva zbog prisutnog posttraumatskog otoka, koji pobuđuju sumnju na eventualno pisustvo vertebralne nestabinsti (**Slika 2**) [12,14].

Indirektno se, dakle, na osnovu nalaza radiografskih lezija povrede vratne kičme može u većini slučajeva odrediti stanje koštanih vertebralnih elemenata kao i diskoligamentarog aparata posle lezije cervikalne kičme [6,15].

Kako se vidi, teorijske postavke vertebralne stabilnosti rezultat su istovremenog delovanja više različitih biomehaničkih faktora. Međutim, mnogobrojna ispitivanja su pokazala da nijedan od uzročnih mehanizama nije sveobuhvatan. Ortoped u savremenoj vertebralnoj traumatologiji teži da koncept spinalne stabilnosti postavi kao dinamičku kategoriju težeći

da se u neposrednoj postraumatskoj fazi predvidi sigurno stabilne, privremeno nestabilne i povrede koje vode ka hroničnoj ili poznoj nestabilnosti. Istraživanja su pokazala da su izolovane frakture prednjeg (A) i zadnjeg (C) vertebralnog stuba stabilne. Frakture srednjeg segmenta (B) akutno su nestabilne. Radi se, međutim, o privremenoj nestabilnosti koja prestaje kada prelom sraste. Postoji još i pojam diskoligamentarne nestabilnosti (D) koji podrazumeva leziju bilo svih prednjih, bilo svih zadnjih mekotkivnih elemenata dinamičkog vertebralnog segmenta. Udružene lezije jednog, dva i tri koštana segmenta i odgovarajuće ligamentarne rupture vode različitim kombinacijama akutne diskoligamentarne nestabinosti (AD, CD, ABD, ACD, ABCD) [4,16-18].

Praktično, sve koštane i inkompletne ligamentarne lezije koje su svrstane u grupu stabilnih (klinaste frakture, frakture apendikularnih nastavaka pršljena), kasnije ne pokazuju sekundarno pomeranje. Rezultirajući entitet je stabilna nestabilnost. To nije slučaj i sa kompresivnim i kominutivnim frakturama koje zahvataju zadnji vertebralni zid pršljena i koje naknadno posle procesa koštanog srastanja pršljena postaju stabilne uz manji ili veći sekundarni angularni deformitet. Nastali entitet se razmatra kao „stabilna nestabilnost". Jasno nestabilne povrede koje imaju neprikrivenu tendenciju da će se naknadno deplasirati (vertebralne frakture praćene limagentarnim kidajem, *tear drop* frakture, hiperekstenzione frakture dislokacije) sa čistom ligamentarnom nestabilnošću (deo prednjih subluksacija i luksacija koje idu s kompletnim ligametarnim kidanjem) imaju snažan potencijal redeplasmana i sekundarnog pomeranja. Taj potencijalni prelazak akutne u hroničnu nestabilnost, zabeležen u ovom radu u 28% slučajeva, definisan je kao „nestabilna nestabilnost".

Na taj način se i definitivno može postaviti dijagnoza preloma pršljena ili kidanja diskoligamentarnog aparata, znajući da kada na profilnim radiografijama postoji određena translacija ili angulacija, već tada možemo govoriti o nestabilnosti posle traume. Oštećenje jednog, dva ili tri koštana mosta (A, B, C) i ligamenata dinamičkog vertebralnog segmenta (D), posmatrano na lateralnim snimcima (kompjuterizovana tomografija i magnetna rezonancija), u visokom procentu omogućava postavljanje dijagnoze povrede i na osnovu toga se stvaraju uslovi za pravilan tretman pacijenta [19,20].

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ORIGINALNI NAUČNI RADOVI
ORIGINAL STUDIES

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NIGHT WORK, TOTAL OCCUPATIONAL BURDEN AND CANCER/CARDIOVASCULAR RISK FACTORS IN PHYSICIANS

NOĆNI RAD, UKUPNO PROFESIONALNO OPTEREĆENJE I FAKTORI RIZIKA ZA NASTANAK MALIGNIH I KARDIOVASKULARNIH OBOLJENJA KOD LEKARA

Karen BELKIĆ[1-3] and Olesja NEDIĆ[4]

Summary

Introduction. Lifestyle-related risk factors: smoking, obesity, sedentariness and excess alcohol intake are among the most important known causes of cancer and cardiovascular disease. The aim of this study is to examine the relationship between these lifestyle-related risk factors for cancer/cardiovascular disease and working conditions among surgeons/anesthesiologists and other physicians. **Material and Methods.** The study was carried out among physicians aged 35 to 60, without diagnosed coronary heart disease or other structural heart disease, who were employed at the Novi Sad University Hospital. The participation rate was high (> 90%). The physicians completed the Occupational Stress Index. Low lifestyle-related cancer/cardiovascular risk was defined as: not a current smoker, body mass index < 28, regular recreational physical activity and not consuming alcohol every day. Analysis of covariance was performed. **Results.** Of 191 physicians included in this study only 23 (12.0%) had a low lifestyle-related cancer/cardiovascular risk. Surgeons/anesthesiologists faced a heavier total work stressor burden than physicians in other profiles (87.7±8.8 versus 74.1±10.5, p=0.000). Among the 56 surgeons/anesthesiologists, lower nightshift work scores were associated with low lifestyle-related cancer/cardiovascular risk (F=4.19, p=0.046). A lower overall work stressor burden was associated with low risk among the other 135 physicians (F=4.06, p=0.046). **Conclusion.** Specific workplace intervention strategies are urgently needed. Among the surgeons/anesthesiologists these should include reduction in the frequency of night call and improvement of the overall conditions of nightshift work. Among other physicians, the total occupational burden needs to be diminished.

Key words: Workplace; Physicians; Occupational Exposure; Stress, Psychological; Risk Factors; Sedentary Lifestyle; Smoking; Obesity; Alcohol Drinking; Body Mass Index; Cardiovascular Diseases; Neoplasms; Work Schedule Tolerance

Sažetak

Uvod. Najveći značaj među mnogim poznatim uzrocima malignih i kardiovaskularnih oboljenja imaju životne navike kao što su pušenje, prekomerna ishrana sa gojaznošću kao posledicom, fizička neaktivnost i prekomerno uzimanje alkohola. Cilj ove studije je da se kod lekara hirurga/anesteziologa i lekara drugih specijalnosti ispita povezanost uslova rada i faktora rizika za nastanak malignih i kardiovaskularnih oboljenja uslovljenih navedenim lošim životnim navikama. **Materijal i metode.** Istraživanje je sprovedeno kod lekara novosadskih klinika i instituta starosti 35−60 godina, sa visokim procentom odaziva (> 90%). Sadašnjom analizom obuhvaćeni su samo lekari bez dijagnostikovanog koronarnog oboljenja, odnosno bez strukturnog oboljenja srca. Lekari su popunili upitnik Indeks profesionalnog stresa (*Occupational Stress Index*). Niži nivo rizika u vezi sa životnim navikama je definisan kao: nepušač, indeks telesne težine < 28, redovna fizička aktivnost i neuzimanje alkohola svakodnevno. Rađena je statistička analiza pomoću analize varijanse i kovarijanse. **Rezultati.** Analizom je obuhvaćen 191 lekar. Svega 23 lekara (12%) imalo je niži nivo rizika. Kod lekara hirurga/anesteziologa utvrđen je veći nivo profesionalnog opterećenja u odnosu na lekare drugih specijalnosti (87,7±8,8 versus 74,1±10,5 p = 0,000). Kod 56 hirurga/anesteziologa manje opterećenje od noćnog rada bilo je povezano sa nižim nivoom rizika (F = 4,19, p = 0,046). Niži ukupan zbir indeska profesionalnog stresa bio je udružen sa nižim nivoom rizika kod ostalih 135 lekara (F = 4,06 p = 0,046). **Zaključak.** Neophodna je urgentna specifična interventna strategija usmerena ka smanjenju učestalosti dežurstava i poboljšanju uslova noćnog rada hirurga/anesteziologa, a kod lekara ostalih specijalnosti neophodno je sniženje ukupne opterećenosti radom.

Ključne reči: Radno mesto; Lekari; Profesionalna izloženost; Stres, psihološki; Faktori rizika; Sedeći način života; Pušenje; Gojaznost; Alkohol; Indeks telesne mase; Kardiovaskularna oboljenja; Karcinomi; Tolerancija na rad u smenama

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Abbreviations

OSI	– Occupational Stress Index
LRCRF	– lifestyle-related cancer and cardiovaskular risk factor
BMI	– body mass index
CVD	– cardiovascular disease

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Introduction

Among the known causes of cancer and cardiovascular disease (CVD), the major proportion has been attributed to lifestyle-related factors. Cigarette smoking accounts for at least 20% of deaths due to cancer and to CVD [1,2]. Obesity is considered to be the leading avoidable cause of cancer among non-smokers, and is an important cause of CVD [3,4]. Alcohol consumption is also a major lifestyle-related cause of cancer [1]. Although there is some evidence that moderate alcohol intake may be cardioprotective, if consumed in larger quantities alcohol contributes to risk of arterial hypertension, cardiomyopathy and cardiac arrhythmias [5]. On the other hand, physical exercise protects against many cancers and against CVD [1,6].

Physicians play a vital role with regard to the lifestyle-related cancer and CVD risk factors (LRCRF) [7]. Notwithstanding these facts, the LRCRF are still very prevalent worldwide, not only in the general population but among physicians, as well. This is the case in Vojvodina and many other regions of the former Yugoslavia [7-10]. Among female university hospital physicians in Novi Sad, the levels of the LRCRF are reported to be inordinately high. It has also been shown that these LRCRF are closely associated with job stressors, as assessed by the Occupational Stress Index (OSI) [7].

In other studies among university hospital physicians in Novi Sad, two OSI dimensions: high demands and threat avoidance were found to be dominant in showing significantly higher exposure levels among physicians with acquired CVD [11,12]. Gender was reported to be a key effect-modifier of the relationship between exposure to work stressors and acquired CVD among these physicians [13].

The deleterious impact of job stressors has been particularly noted among surgeons and anesthesiologists. These physician profiles have been associated with high levels of work-related burnout, psychological distress and high overall mortality rates [14-18]. Long work hours and number of nights on-call have been implicated as job stressors eliciting distress among surgeons and anesthesiologists [19,20]. In these physician profiles, gender emerges once again as a key-effect modifier with regard to job stressors [21]. Nyssen and colleagues [16] note, however, that very diverse approaches have been used to assess job stressors among surgeons and anesthesiologists.

The OSI provides a theoretically-coherent and practical approach for a comprehensive, quantitative assessment of job stressors among physicians as well as for a number of other occupations in various countries [22-26]. The OSI for physicians has been applied among a wide range of surgical and non-surgical clinical specialties as well as among diagnostic and preventive branches of medicine, and captures both the within- and between-group variation in working conditions. The OSI for physicians is especially helpful for identifying modifiable work stressors among these various branches of medicine [24].

In light of the above-outlined background information, the present study has the following objectives and hypotheses. First, we aim to compare the working conditions of surgeons and anesthesiologists with other Novi Sad University Hospital physicians, using the OSI. Our hypothesis is that the surgeons and anesthesiologists will show a substantially higher burden of job stressors, particularly with regard to job demands and threat avoidant vigilance. Our second aim is to assess whether any associations can be identified between job stressors faced by surgeons and anesthesiologists and the above mentioned lifestyle related risk factors. In particular, we seek to identify modifiable stressors that could be the focus for interventions. We hypothesize that job stressors related to work schedule (long work hours and/or night shift work) will show a relation to the LRCRF among surgeons and anesthesiologists. Finally, we aim to assess the effect of gender upon the relations among physician profile, job stressors and the LRCRF. Our hypothesis is that the associations between job stressors and the LRCRF will be most pronounced among female physicians.

The importance of the present study is even higher because it is carried out in Novi Sad, where, as stated, the level of LRCRF is exceedingly high among physicians as well as among the general population. The need is therefore urgent to identify strategies that could most effectively help reduce this risk.

Material and Methods

Design of the Study

The present study is cross-sectional, and was carried out among physicians employed and actively working at the Novi Sad University Clinical Center [11]. Other eligibility criteria were age between 35 and 60, and receiving primary health care services at the Novi Sad Occupational Health Center. In the present analysis, only physicians without a history of myocardial infarction or documented coronary artery disease were included. Other structural CVD or secondary hypertension were exclusion criteria for the entire study [11].

Each physician who fulfilled the entry criteria was invited to participate in the study. He/she was given the following information: (i) the study was

Table 1. The Occupational Stress Index [23] reprinted with permission
Tabela 1. *Indeks profesionalnog stresa [23] sa dozvolom autora*

Aspects Levels *Aspekti Nivoi*	Underload *Podopterećenje*	High Demand *Visoki zahtevi*	Strictness *Strogost-tačnost*	Time pressure *Spoljašnji vremenski pritisak*	Exposure to noxins *Izloženost noksama*	Avoidance/Symbolic Aversiveness/*Averzivnost/Izbegavanje opasnosti*	Conflict/Uncertainty *Konflikti/Neizvesnost*
Input *Primanje informacija*	• Homogeneous signals/*Istovrsne informacije* • Low frequency of incoming signals *Retko pristizanje novih signala* • Works alone-without need for communication *Radi sam bez potrebe za komunikacijom*	• Several information sources/*Više izvora informacija* • Heterogeneous information/*Raznorodne informacije* • Heavy burden on visual system/*Primarno vizuelno opažanje* • High frequency of incoming signals/*Visok tok novih informacija* • 3 sensory modalities/*3 čulna nadražaja istovremeno* • Communication essential/*Neophodnost komunikacije pri radu*	• Strict requirements for signal detection *Strogi zahtevi za tačnost u detekciji signala*	• No control over speed of incoming signals *Ne kontroliše brzinu pristižućih informacija*	• Glare *Bljesak* • Noise *Buka*	• High level of attention (Serious consequences of momentary lapse) *Visok nivo trajne pažnje/ nesagledive posledice momentalnog pada nivoa pažnje* • Visually-disturbing scenes/*Izloženost vizuelno uznemirujućim scenama* • Listens to emotionally-disturbing occurrences/ *Izloženost emocionalno uznemirujućim događajima*	• Signal/noise conflict *Nejasna razlika između šuma i signala* • Signal/signal conflict *Nejasna razlika između različitih signala*
Central Decision-Making *Donošenje odluka*	• Decisions automatic from input *Odluke slede automatski na osnovu primljenih informacija*	• Complex decisions *Složene odluke* • Complicated decisions *Komplikovane odluke* • Decisions affect work of others *Odluke utiču na rad drugih* • Rapid decision-making *Donošenje brzih odluka*	• Strict problem-solving strategy *Ograničenja u pristupu odlučivanja* • Strictly-defined correct decision/ *Strogo ograničen broj tačnih odluka*	• Decisions cannot be postponed *Odluke se ne mogu odložiti*		• Serious (potentially fatal) consequences of a wrong decision *Teške (eventualno smrtonosne) posledice pogrešnih odluka*	• Missing information needed for decision/*Nedostatak informacija za donošenje odluka* • Contradictory information *Protivrečne informacije* • Unexpected events change work plan/*Novi plan rada zbog nepredviđenih događaja*
Output Task Performance *Izvršavanje zadataka*	• Homogeneous tasks *Istovrsni zadaci* • Simple Tasks *Jednostavni zadaci* • Nothing to do *Nedovoljan posao - nema ništa da radi*	• Heterogeneous tasks *Raznorodni zadaci* • Simultaneous task performance/*Istovremeno izvršavanje zadataka* • Complex tasks *Složeni zadaci* • Rapid task performance *Brzo izvršavanje zadataka*	• Work must meet a strictly-defined standard *Stroga kontrola rada po pravilima*	• No control over rate of task performance *Nema uticaja na tempo rada*	• Isometric lifting *Dizanje tereta* • Vibration *Vibracije*	• Hazardous task performance *Akutne opasnosti pri radu*	• Conflicting demands *Protivrečni zadaci* Task performance hampered by/*Ometanje rada zbog:* • Extrinsic problems *Spoljašnjih problema* • Interruptions from people/ *Prekidi od strane saradnika (ljudi)*
General Opšti	• Fixed pay *Fiksna plata* • Inadequate pay *Neadekvatna plata* • No chances for upgrade *Nemogućnost napredovanja u karijeri* • Lack of recognition of work *Nedostatak priznanja za rad*	• Piece rate work *Plata po učinku* • Long work hours *Dugo radno vreme* • Holds 2+ jobs *Honorarni rad* • Lack of rest breaks *Nedostatak pauze u toku rada* • Night shift work *Noćni/smenski rad* • Lack of paid vacations *Nedostatak plaćenog odmora*	• Fixed body position/*Fiksiran telesni položaj* • Confined workspace/*Sužen radni prostor* • Lack of autonomous workspace/ *Nema sopstvenog radnog prostora* • Limited in taking time off from work/*Ograničene mogućnosti uzimanja slobodnih dana/sati* Low influence over/*Ograničen uticaj na:* • Schedule/*Radni razpored* • Tasks *Zadatke* • Policy/*Politiku ustanove* • With whom one works/*Izbor saradnika*	• Deadline pressure *Rad vezan za vremenski rok* • Speed-up *Ubrzavanje rada*	• Heat *Visoka temperatura* • Cold *Niska temperatura* • Gases, fumes, dusts *Gasovi, pare, prašine*	• Work Accident *Doživene povrede na radu* • Witnessed work accident *Svedok povrede na radu* • Suicide occurrence *Samoubistvo u okviru rada* • Work-related litigation/Testifying in court *Parničenje na sudu* • Lack of functioning emergency system *Nedostatak sistema za slučaj opasnosti*	• Emotionally-charged work atmosphere *Emocionalno opterećena radna atmosfera-konflikti* • Lack of help with work-related difficulties *Nedostatak pomoći od kolega* • Opposition to career advancement *Protivljenje unapređenje u karijeri* • Violations of behavior norms/abuses of power/*Kršenje normi ponašnja/zloupotreba vlasti* • No grievance redress *Nema načina žalbe* • Threat of job loss *Pretnja otpuštanjem* • Job lacks coherence *Posao bez smisla*

designed to evaluate physician working conditions and health within the framework of participatory action research [27], i.e. "*by-physicians-for-physicians*", (ii) the study entailed completing a questionnaire about the physician's job conditions, habits and sociodemographics, and the Minnesota Multiphasic Personality Inventory [28], (iii) participation included permission to consult the physician's medical records in order to verify questionnaire data, (iv) the participants were completely free to withdraw from the study at any time without any consequences whatsoever, and (v) all information would be handled in a totally confidential manner. All participants gave informed consent. The study was carried out from 2002 to 2004 and was approved by the Novi Sad Medical School Ethics Committee.

Independent Variables and Covariates

Sociodemographic Variables: Age, gender, length of service as a physician and medical specialty were noted. The latter was categorized as: 1) surgeons or anesthesiologists, 2) other branches of medicine: non-surgical clinical-care or diagnostic/preventive (e.g. radiologists, pathologists, medical hygiene, etc.).

Job Stressors: These were assessed by the validated Serbian version [23,26] of the physician-specific OSI questionnaire. The physicians were asked to answer the questions about job conditions over the past 10 years, or for as long as they had been employed as physicians if less than 10 years. Additive scores for the aspects and the total OSI were calculated, according to the OSI model (**Table 1**). For further details about the OSI for physicians, including its validity and reliability, see Refs. [7,23]. The OSI questionnaire data about workhours, nightshifts, vacations, moonlighting, physical/chemical exposures, performance of invasive procedures and emergency work were cross validated by medical records, expert observations and worksite measurements [11].

Outcome Variable

Lifestyle-related Risk Factors for Cancer and CVD: The physicians were asked whether they currently smoked cigarettes and if yes, the number of cigarettes smoked per day. The body mass index (BMI) was calculated according to the reported height and weight. Medical records were reviewed to cross-validate questionnaire data about smoking, obesity and alcohol consumption. A query was made about regular recreational physical activity (at least once per week). A composite dichotomous variable was then created: low lifestyle-related cancer or cardiovascular risk factors, i.e. low LRCRF. This was defined as: not a current smoker, BMI < 28, regular recreational physical and no daily alcohol consumption.

Statistical Analysis

Sociodemographic variables and BMI were compared using 2-way analysis of variance (ANOVA). The between group factors were gender and surgeons/anesthesiologists versus other specialties. The other lifestyle-related risk factors, including the composite LRCRF index were treated as dichotomous variables and differences between male and female physicians and between surgeons/anesthesiologists versus other specialties were assessed using χ^2 analyses without Yates correction. The differences among the physicians with regard to individual job stressors, the OSI aspects as well as the total OSI were evaluated with 2-way analysis of covariance (ANCOVA). The between group factors were gender and surgeons/anesthesiologists versus other specialties, and age was treated as a covariate.

Testing was then performed to identify job stressors that were associated with the outcome variable: low lifestyle-related risk among the surgeons/anesthesiologists and among the physicians of other specialties. This stratified analysis was done using ANCOVA, with age as a covariate. STATISTICA software was used throughout.

Results

The participation rate in the study was over 90%, as we previously reported [11,12]. **Table 2** presents the sociodemographic characteristics and lifestyle related risk for cancer and IHD. The male physicians had a significantly higher BMI and more of them consumed alcohol daily than the female physicians. The BMI was significantly lower among the surgeons/anesthesiologists compared to other physicians. No interaction effects were found between physician group and gender. There were no significant between group differences in the outcome variable, low LRCRF.

The OSI aspects and total OSI scores are shown in **Table 3.** The surgeons/anesthesiologists had significantly higher scores for underload, high demand, strictness, noxious exposures and threat avoidant vigilance, as well as for total OSI. High demands, threat avoidant vigilance and total OSI scores were significantly higher among the male physicians. No interaction effects were found between physician group and gender.

We identified the following modifiable job stressors that contributed to the higher demand scores among the surgeons/anesthesiologists compared to other physicians: long work hours: $F = 4.81$, $p = 0.03$ and night shift work: $F = 22.7$, $p = 0.000004$, adjusting for age and gender as covariates. Extent of exposure to emotionally-disturbing occurrences was identified as a potentially modifiable job stressor contributing to the higher burden of threat avoidant vigilance among the surgeons/anesthesiologists compared to other physicians, $F = 5.2$, $p = 0.02$, adjusting for age and gender as covariates.

The top panel of **Table 4** shows that for the surgeons/anesthesiologists, lower night shift work scores were significantly associated with low lifestyle-related cancer or cardiovascular risk. In gender-stratified analysis, this association was significant among the female surgeons/anesthesiologists ($F=4.69$, $p=0.039$). However, this association was not statistically significant among the male surgeons/anesthesiologists, among whom only three had a low LRCRF.

Table 2. Lifestyle-related cancer or cardiovascular risk factors and other characteristics of the 4 groups of physicians (University Clinical Center of Vojvodina)
Tabela 2. *Faktori rizika uslovljeni lošim životnim navikama za nastanak malignih i kardiovaskularnih oboljenja i sociodemografski podaci kod 4 grupe lekara (Klinički centar Vojvodine)*

	Male physicians *Lekari muškog pola*		Female physicians *Lekari ženskog pola*		Significant effect *Statistički značajan nalaz*	P level if < 0.05 *Nivo značajnosti ukoliko P < 0.05*
	Surgeons or anesthesiologists group *Hirurzi/ Anesteziolozi* N = 24	Other branches *Ostale specijalnosti* N = 58	Surgeons or anesthesiologists group *Hirurzi/ anesteziolozi* N = 32	Other branches *Ostale specijalnosti* N = 77	• Surgeons or anesthesiologists group *Hirurzi/ anesteziolozi* • Gender *Pol*	
	$\bar{x} \pm \sigma$ (Range/*Opseg)*	$\bar{x} \pm \sigma$ (Range/*Opseg)*	$\bar{x} \pm \sigma$ (Range/*Opseg)*	$\bar{x} \pm \sigma$ (Range/*Opseg)*		
Age/*Starosti*	48.8±7.0 (37–60)	49.0±7.5 (35–60)	45.8±8.4 (35–60)	49.9±5.7 (35–60)		NS
Length of service as a physician/*Radni staž kao lekara* 1 = < 10 y *godina* 2 = 10 – 19 y/*godina* 3 = 20 – 29 y/*godina* 4 = 30 y/*godina*	2.7±0.9 (1–4)	2.7±0.9 (1–4)	2.5±1.0 (1–4)	2.9±0.7 (1–4)		NS
Body mass indeks *Indeks telesne težine*	27.2±3.0 (22.0–34.6)	27.6±3.0 (22.5–37.0)	23.4±2.8 (18.0–29.4)	25.5±4.1 (18.0–37.2)	• Surgeons or anesthesiologists group *Hirurzi/ anesteziolozi* • Gender/*Pol*	0.03 0.000
	N (%)	N (%)	N (%)	N (%)		
Current smoker *Sadašnji pušač*	9 (37.5%)	14 (24.1%)	13 (40.6%)	22 (28.6%)		NS
Heavy smoker (>20/day) *Strastven pušač (>20 dnevno)*	4 (16.7%)	5 (8.6%)	4 (12.5%)	6 (7.8%)		NS
Body mass indeks <28 *Indeks telesne težine* <28	8 (33.3%)	21 (36.2%)	3 (9.4%)	18 (23.4%)	• Gender *Pol*	0.01
Daily alcohol consumption *Svakodnevno uzimanje alkohola*	8 (33.3%)	23 (39.7%)	1 (3.1%)	5 (6.5%)	• Gender *Pol*	0.000
Regular physical activity (≥ once/week) *Redovne fizičke aktivnosti (≥jednom nedeljno)*	9 (37.5%)	18 (31.0%)	10 (31.3%)	15 (19.5%)		NS
Low LRCRF/*Niski RFLZN*	3 (12.5%)	5 (8.6%)	7 (21.9%)	8 (10.4%)		NS

Analysis of variance, with 2 between group factors (physician group & gender) for age, lenght of service as a physician and body mass index/*Urađena je analiza varijanse sa 2 faktora (vrsta lekara i pol) za godine starosti, radni staž kao lekar i indeks telesne težine;* χ^2 analyses performed for the remaining variables/*Urađen je* χ^2 *test za ostale promenljive*

Low LRCRF= lifestyle-related cancer or cardiovascular risk factors, defined as: not a current smoker, BMI < 28, regular recreational physical activity and no daily alcohol consumption/*Niski RFLZN = nizak nivo faktora rizika za nastanak malignih i kardiovaskularnih oboljenja uslovljenih lošim životnim navikama t.j. nepušač, indeks telesne težine < 28, redovna fizička aktivnost, neuzimanje alkohola svakodnevno;* σ = standard deviation/*standardna devijacija;* NS = statistically non-significant/*statistički bez značajnosti (P ≥ 0.05)*

Among the physicians in other branches, a lower total OSI score showed a significant association with LRCRF, as seen in the bottom panel of **Table 4**. In gender-stratified analysis, this association was significant among the female physicians in the other branches (F=7.51, p=0.008). However, this association was not statistically significant among the male physicians in other branches, among who only five had a low LRCRF.

Table 3. The aspects and total OSI among the 4 groups of physicians (University Clinical Center of Vojvodina)
Tabela 3. *Aspekti i ukupan indeks profesionalnog stresa kod 4 grupe lekara (Kliničkog centra Vojvodine)*

OSI Aspect *Aspekti indeksa profesionalnog stresa*	Male physicians *Lekari muškog pola*		Female physicians *Lekari ženskog pola*		Significant effect *Statistički značajan nalaz* • Surgeons or anesthesiologists group *Hirurzi/ anesteziolozi* • Gender/*Pol*	P level if < 0.05 *Nivo značajnosti ukoliko P < 0.05*
	Surgeons or anesthesiologists group *Hirurzi/ anesteziolozi* N = 24	Other branches *Ostale specijalnosti* N = 58	Surgeons or anesthesiologists group *Hirurzi/ anesteziolozi* N = 32	Other branches *Ostale specijalnosti* N = 77		
	$\bar{x} \pm \sigma$ (Range/*Opseg)*	$\bar{x} \pm \sigma$ (Range/*Opseg)*	$\bar{x} \pm \sigma$ (Range/*Opseg)*	$\bar{x} \pm \sigma$ (Range/*Opseg)*		
Underload *Podopterećenje*	3.7±1.4 (0–6)	3.3±1.2 (0–6)	3.8±0.9 (2–6)	3.4±0.8 (1–5)	• Surgeons or anesthesiologists group *Hirurzi/anesteziolozi*	0.006
High demand *Visoki zahtevi*	32.0±3.5 (18–34.8)	26.4±4.6 (16.5–34.3)	29.7±3.5 (17.8–34)	24.7±4.9 (15.8–33.5)	• Surgeons or anesthesiologists group *Hirurzi/anesteziolozi* • Gender/*Pol*	0.000 0.003
Strictness *Ograničenja*	16.3±2.4 (9–19.5)	13.2±2.7 (6.3–19)	16.4±2.1 (11.8–8.5)	13.7±2.7 (6–18)	• Surgeons or anesthesiologists group *Hirurzi/anesteziolozi*	0.000
External time pressure *Spoljašnji vremenski pritisak*	7.8±1.1 (5–9.5)	7.8±1.3 (5–10)	8.3±1.4 (4.5–10)	7.7±1.2 (5–10)		NS
Noxious exposures *Izloženost noksama*	4.6±1.3 (3–7)	1.1±1.3 (0–5.5)	3.8±1.4 (1.5–7.5)	1.1±1.2 (0–5)	• Surgeons or anesthesiologists group *Hirurzi/anesteziolozi*	0.000
Threat avoidant vigilance *Izbegavanje opasnosti*	10.9±2.4 (6–16)	9.9±2.8 (4–15.5)	9.9±1.7 (5.5–13.5)	8.4±2.5 (4–16)	• Surgeons or anesthesiologists group *Hirurzi/anesteziolozi* • Gender/*Pol*	0.003 0.002
Conflict/uncertainty *Konflikti/neizvesnost*	14.4±2.1 (10.5–18.5)	13.5±2.5 (8.5–18.5)	14.2±2.2 (9.5–18)	14.3±2.6 (8.5–22)		NS
Total OSI *Ukupan indeks profesionalnog stresa*	89.8±8.0 (67–98.5)	75.2±10.2 (52.8–93.3)	86.1 ± 9.2 (63.3–101.3)	73.3±10.7 (46.8 – 103.3)	• Surgeons or anesthesiologists group *Hirurzi/anesteziolozi* • Gender/*Pol*	0.000 0.047

Analysis of covariance, with 2 between group factors (physician group & gender) adjusted for age./*Urađena je analiza kovarijanse sa 2 faktora (vrsta lekara i pol) korigovano za starost;* OSI = occupational stress index/*indeks profesionalnog stresa*; σ = standard deviation/*standardna devijacija*; NS = statistically non-significant/*statististički bez značaja* $P \geq 0.05$

Discussion

As hypothesized, the mean total OSI scores among the surgeons and anesthesiologists were significantly higher than those of the physicians in other profiles. The significance level was maximal. This indicates that the overall burden of job stressors is much heavier for surgeons and anesthesiologists. Many of the standard deviations were also smaller and the ranges narrower. Notably, the minimum values of the total OSI scores were well over 10 points higher among the surgeons and anesthesiologists.

It was not only the high demand and threat avoidant aspects that were significantly higher among the surgeons and anesthesiologists, as hypothesized. This was also the case for the underload, strictness and noxious exposures aspects. For nearly all of these aspects, the standard deviations were smaller and the minimum values higher. These findings reflect not only the urgent nature of the work, but also heavier exposures to physical and chemical noxins, more complex task performance, stricter requirements for signal detection, fixed body position, the need to maintain maximally high vigilance and more frequent encounters with trauma and other visually disturbing scenes, *inter alia*. Taken together, these findings are consistent with the fact that a large number of the stressors faced by surgeons and anesthesiologists are integral to their work profile *per se* and that the possibilities for readily implementable modifications are rather limited.

Table 4. Indicators of low lifestyle-related cancer or cardiovascular risk* among the two groups of physicians (University Clinical Center of Vojvodina)
Tabela 4. *Indikatori niskog nivoa faktora rizika za nastanak malignih i kardiovaskularnih oboljena uslovljenih lošim navikama* kod dve grupe lekara (Kliničkog centra Vojvodine)*

Surgeons or anesthesiologists/*Lekari specijalisti hirurzi i anesteziolozi*

Analysis of Covariance *Analiza Kovarijanse* F = 4.19 p =0.046 (Adjusted for age)/*(korigovano za starost)*		Number *Broj lekara*	OSI Night Shift Work Score *Nivo opterećenja noćnim radom prema indeksu profesionalnog stresa* $\bar{x} \pm \sigma$
Low Lifestyle-Related Risk *Nizak nivo faktora rizika uslovljenih lošim navikama*	Yes/*Da*	10	1.25±0.87
	No/*Ne*	46	1.70±0.55

Physicians in other branches (Other than surgeons or anesthesiologists)
Lekari drugih specijalnosti (lekari koji nisu hirurzi ili anesteziolozi)

Analysis of Covariance/*Analiza Kovarijanse* F = 4.19 p =0.046 (Adjusted for age)/*(korigovano za starost)*		Number *Broj lekara*	Total OSI score *Ukupan indeks profesionalnog stresa* $\bar{x} \pm \sigma$
Low Lifestyle-Related Risk *Nizak nivo faktora rizika uslovljenih lošim navikama*	Yes/*Da*	13	68.2±10.3
	No/*Ne*	122	74.8±10.3

*Low life-style related cancer or cardiovascular risk factors, defined as: not a current smoker, BMI < 28, regular recreational physical activity and not consumption of alcohol daily
**Niski faktori rizika za nastanak malignih i kardiovaskularnih oboljena uslovljenih lošim navikama definisani kao: nepušač, indeks telesne težine < 28, redovne fizičke aktivnosti, neuzimanje alkohola svakodnevno*

Of the more readily modifiable job stressors faced by surgeons and anesthesiologists, mean scores for long work hours, nightshift work and extent of exposure to emotionally disturbing occurrence were found to be significantly higher compared to the other physicians. It was night shift work that differed most markedly between the two groups. Of greatest importance for the present study, nightshift work score was identified as a significant multivariate correlate of lifestyle-related cancer/CVD risk factor status, LRCRF. Namely, the likelihood that a surgeon or anesthesiologist is a non-smoker, not overweight, not consuming alcohol every day and engaging regularly in recreational physical activity appears to be related to conditions of nightshift work. In the specific OSI for physicians, the nightshift work score reflects not only the frequency of night call but also the free time before and after night call, as well as whether there is guaranteed relief, so that the physicians can be certain that their patients will be cared for by other colleagues [23]. These conditions can be regulated quite easily through careful attention and planning. The benefits of such measures for health professionals have been demonstrated with respect to biomarkers of cardiovascular risk [29,30]. It should also be emphasized that there are reported associations between nightshift work among health professionals and risk of specific cancers, even after adjusting for life-style related risk factors [31,32]. There is also a well-established link between shift-work and CVD [33,34], especially among women [35].

For the physicians in other branches, it was the total job stressor burden that showed a significant relation to LRCRF status. Since there are more potentially modifiable factors, interventions aimed at the LRCRF could be more flexibly developed, based upon actual conditions. It is our experience that interventions aimed at lifestyle-related risk factors are most successful when coupled to amelioration of the overall job stressor burden, as reflected by the total OSI [36,37].

It was among the female physicians in both groups that the associations between job stressors and LRCRF were most clearly demonstrated. However, the total OSI scores were significantly higher among the male physicians and though non-significant, percentually fewer male physicians were classified as having a low LRCRF. Thus, it may be that there was insufficient power in the present study to identify a gender-specific relation between work stressors and LRCRF among the male physicians.

Limitations of the Study

Since only actively working physicians were eligible, there is a possible selection of those who were relatively healthy. This is likely to bias the results towards the null [38]; therefore, the associations may have been underestimated. We used cutoff values for several of the lifestyle-related risk factors. This could possibly lead to non-differential misclassification, which could also bias the results towards the null [38].

On the other hand, since the present study is cross-sectional, inferences about the temporal nature of observed associations should be made with caution.

There has been some time lag since the data were collected. However, in our clinical judgment, this is unlikely to have affected the findings.

The above-mentioned insufficiency in the power is another limitation of the present study, and underscores the need for replication. Randomized intervention trials in which the work stressors are ameliorated would be a practical way to further examine their etiologic association with the evaluated risk behaviors, and at the same time test the efficacy of prevention strategies.

Conclusion

Surgeons and anesthesiologists face a heavier work stressor burden than physicians in other profiles. Relatively fewer of the job stressors are amenable to amelioration. Among the more readily modifiable stressors in the work environment of surgeons and anesthesiologists, nightshift work is identified for its adverse impact upon lifestyle-related risk of cancer and cardiovascular disease. The conditions of nightshift work should therefore be a specific target of interventions aimed at lowering this risk among surgeons and anesthesiologists. Among physicians in other profiles, our results demonstrate a deleterious relation between the overall job stressor burden *per se* and lifestyle-related risk of cancer and cardiovascular disease. This suggests the need and possibility for broader intervention strategies in which the work environment and risk behaviors are targeted. Lifestyle-related risk of cancer and cardiovascular disease is very high among physicians working at the Novi Sad University Hospital. This underscores the urgent need for preventive measures among physicians in this high-risk region.

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PHYSICAL FITNESS IS INVERSELY RELATED WITH BODY MASS INDEX AND BODY FAT PERCENTAGE IN SOCCER PLAYERS AGED 16-18 YEARS

FIZIČKA KONDICIJA JE OBRNUTO SRAZMERNA INDEKSU TELESNE MASE I PROCENTU TELESNE MASNOĆE KOD FUDBALERA STARIH 16-18 GODINA

Pantelis THEODOROS NIKOLAÏDIS

Summary
Introduction: Adolescents are at increased risk for the development of obesity, while sport has been suggested as an effective means against adolescent obesity. The objectives of this study were to examine (a) the prevalence of overweight/obesity, (b) the relationship between body mass index and body fat percentage, and (c) the association between body mass index, body fat and physical fitness in soccer players aged 16-18 yr. **Material and Methods:** Members (n=109, aged 17.0±0.5 yr) of competitive soccer clubs were examined for physical and physiological characteristics. **Results**: Based on international body mass index cut-off points, 18.3% (n=20) of participants were classified as overweight. Body mass index was highly correlated with body fat percentage (r=0.70, p<0.001). Body fat percentage was in inverse relationship with aerobic power (r=-0.21, p=0.029), maximal anaerobic power (r=-0.20, p=0.044) and local muscular endurance (r=-0.39, p<0.001), while corresponding values of body mass index were non-significant (r=-0.05, p=0.614; r=0.03, p=0.771; r=-0.12, p=0.220, respectively). However, both body fat percentage and body mass index were inversely related with fatigue index of Wingate anaerobic test (r=-0.26, p=0.009; r=-0.29, p=0.003, respectively). **Conclusions:** The strong relationship between body mass index and body fat percentage suggest the further use of body mass index in adolescent soccer players. The findings confirmed previous observations on general population about the negative effect of overweight and fatness on physical fitness. The prevalence of overweight among participants was similar with what is observed in general population. Therefore, sport participation cannot guarantee physiological body mass and body composition, and it is necessary to prescribe exercise targeting body mass and fat control.
Key words: Body mass index; Physical exercise; Sport; Adolescent

Sažetak
Uvod: Adolescenti imaju povećani rizik od nastanka debljine, a sport se predlaže kao efikasno sredstvo u borbi protiv debljine adolescenata. Cilj ove studije je bio da ispita (a) rasprostranjenost prekomerne težine/debljine, (b) odnos između indeksa telesne mase i procenta telesne masnoće i (c) vezu između indeksa telesne mase, telesne masnoće i fizičke kondicije kod fudbalera starih od 16 do 18 godina. **Materijal i metode:** Ispitivane su fizičke i fiziološke karakteristike članova takmičarskog fudbalskog kluba (n=109, godine starosti 17±0,5. **Rezultati:** Na osnovu internacionalnih graničnih vrednosti indeksa telesne mase, 18,3% (n=20) učesnika su klasifikovani kao osobe sa prekomernom težinom. Indeks telesne mase bio je izrazito povezan sa telesnom masnoćom (r=0,70, p<0,001). Telesna masnoća je bila u obrnutom odnosu sa aerobnom snagom (r=-0,21, p=0,029), maksimalnom anaerobnom snagom (r=-0,20, p=0,044) i lokalnom mišićnom izdržljivosti (r=-0,39, p<0,001), dok odgovarajuće vrednosti indeksa telesne mase nisu bile značajne (r=-0,05, p=0,614; r=0,03, p=0,771; r=-0,12, p=0,220)). Međutim, i telesna masnoća i indeks telesne mase bili su obrnuto srazmerni sa indeksom umora Wingate anaerobnog testa (r=-0,26, p=0,009 tj. r=-0,29, p=0,003). **Zaključak:** Jaka veza između indeksa telesne mase i telesne masnoće ukazuje na dalju upotrebu indeksa telesne mase kod fudbalera adolescentata. Ti nalazi su potvrdili prethodne opservacije o negativnom efektu prekomerne težine i debljine na fizičku kondiciju kod opšte populacije. Rasprostranjenost prekomerne težine među učesnicima bila je slična onoj koja se primećuje kod opšte populacije. Stoga, bavljenje sportom ne može da garantuje fiziološku telesnu masu i telesni sastav, pa je neophodno propisati ciljane vežbe za kontrolu telesne mase i masnoće.
Ključne reči: Indeks telesne mase; Fizičke vežbe; Sport; Adolescent

Introduction

Obesity and overweight in adolescence represent an important public health issue [1]; it has been suggested that they can be tracked from childhood and adolescence to adulthood, and are linked to many other diseases [2,3]. While sport is a promising setting for obesity prevention, the re-levant research has revealed controversial results [4]. Although soccer is the most widely practiced sport in Europe [5], no

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Abbreviations

BMI	– body mass index
BF	– body fat
SAR	– sit-and-reach test
PWC170	– physical working capacity at heart rate 170 beats/min

study has ever been conducted so far to investigate the prevalence of overweight and obesity in young male soccer population and their impact on physical fitness.

Body mass index (BMI) is employed globally to classify humans as normal, overweight and obese [6]. Even though BMI has several limitations as an assessment method of body composition (e.g., it cannot identify sarcopenic obesity [7]), it is inexpensive and easy to administer. However, its application in sport population has been questioned [8], because it is associated with fat mass as well as with fat free mass. For instance, as BMI is increased by high amounts of both fat and fat free mass, a very muscular athlete with low BF could be classified as overweight. Recent studies have shown that the relationship between BMI and BF is influenced by sex, age and sport [4,9,10]. Such relationship has not yet been identified in adolescent soccer players. If BMI was in strong correlation with BF, it would offer the coach, trainer or other allied health care professional engaged in soccer training an important tool to develop proper exercise programs.

In addition to their implications for health, BF and BMI are associated with reduced physical fitness, as it has been indicated by research conducted chiefly on general population [10-13]. In the aforementioned research, the comparison between groups of general population with different BMI has revealed that the groups with lower or normal BMI perform better in physical fitness tests than overweight/obese or those with higher BMI. However, such associations have not yet been investigated in youth soccer. Therefore, the objectives of this study were to examine (a) the prevalence of overweight/obesity, (b) the relationship between BMI and BF, and (c) the association between BMI, BF and physical fitness in soccer players aged 16-18 years.

Material and Methods

In this investigation, a descriptive-correlation design was used to examine the association between BMI, BF and physical fitness. Young male soccer players (n=109, aged 17.0±0.5 yr, weight 69.1±9.3 kg, height 1.76±0.06 m, BMI 22.4±2.5 $kg \cdot m^{-2}$ and BF 15.8±3.5%), all members of competitive sport clubs, volunteered for this study. They had 6.5±2.8 years of training experience and were engaged in soccer training 4.2±1.1 days weekly with each session lasting 1.6±0.4 h, i.e. a total weekly training volume of 6.6±2.2 h. Oral and written informed consent was received from all participants or parents after verbal explanation of the experimental design and potential risks of study. Height, body mass and skin-folds were measured, BMI was calculated as the quotient of body mass (kg) to height squared (m^2), and BF was estimated from the sum of 10 skin-folds [14]. The electronic weight scales (HD-351 Tanita, Illinois, USA) were employed for body mass mea-surement (in the nearest 0.1 kg), a portable stadiometer (SECA, Leicester, UK) for stature (1 mm) and a caliper (Harpenden, West Sussex, UK) for skin-folds (0.5 mm). All participants performed the following physical fitness tests in the respective order:

(a) Sit-and-reach test (SAR). The SAR protocol [15] was employed for the assessment of low back and hamstring flexibility.

Table 1. Anthropometric and physiological characteristics of BMI quartile groups
Tabela 1. *Antropometrijske i fiziološke karakteristike kvartilnih grupa indeksa telesne mase*

	Quartiles of BMI/*Kvartili indeksa telesne mase*					
	1st (n = 27)	2nd (n = 28)	3rd (n = 27)	4th (n = 27)	ANOVA	Bonferroni test
Age (yr)/*Starost (godine)*	16.9±0.6	17.2±0.5	17.0±0.6	17.0±0.5	F3,105 = 2.15, p = 0.098	
BM (kg)/*Telesna masa*	59.7±4.9	66.7±4.4	70.9±4.5	79.0±9.7	F3,105 = 44.67, p < 0.001	Q1<Q2<Q3<Q4
Height (m)/*Visina*	1.75±0.07	1.76±0.06	1.76±0.06	1.75±0.08	F3,105 = 0.08, p = 0.974	
BMI (kg/m^2) *Indeks telesne mase*	19.4±1.1	21.6±0.5	23.0±0.4	25.7±1.7	F3,105 = 168.62, p < 0.001	Q1<Q2<Q3<Q4
BF (%)/*Telesna masnoća*	12.5±1.7	15.2±2.3	16.1±3.0	19.4±3.0	F3,105 = 34.00, p < 0.001	Q1<Q2<Q3<Q4
SAR (cm)/*Sedi i dohvati*	22.1±6.1	23.7±7.4	23.6±6.8	23.5±6.2	F3,103 = 0.33, p = 0.802	
PWC170 ($W \cdot kg^{-1}$) *Fizički radni kapacitet*	2.6±0.4	2.6±0.4	2.7±0.6	2.5±0.3	F3,104 = 1.34, p = 0.267	
Pmax ($W \cdot kg^{-1}$) *Maksimalna snaga*	14.2±2.4	14.6±3.2	14.6±2.2	14.5±3.2	F3,98 = 0.09, p = 0.965	
Pmean ($W \cdot kg^{-1}$) *Srednja snaga*	8.8±0.6	8.7±0.5	8.9±0.7	8.4±0.7	F3,98 = 3.40, p = 0.021	Q3>Q4
FI (%)/*Indeks umora*	37.1±7.7	43.8±8.6	42.8±7.2	44.1±7.9	F3,98 = 4.34, p = 0.006	Q1<Q2, Q1<Q4

BM-body mass, Pmax maximal power, Pmean mean power, FI fatigue index and Q quartile group

Table 2. Anthropometric and physiological characteristics of BF quartile groups
Tabela 2. *Antropometrijske i fiziološke karakteristika kvartilnih grupa telesne masnoće*

	Quartiles of BF/*Kvartili telesne masnoće*					
	1st (n = 27)	2nd (n = 28)	3rd (n = 27)	4th (n = 27)	ANOVA	Bonferroni test
Age (yr)/*Starost (godine)*	17.0±0.6	17.1±0.6	17.1±0.5	17.0±0.5	F3,105 = 0.22, p = 0.883	
BM (kg)/*Telesna masa*	62.5±5.7	63.8±5.7	72.7±6.2	77.5±9.8	F3,105 = 28.47, p < 0.001	Q1,Q2<Q3,Q4
Height (m)/*Visina*	1.75±0.06	1.73±0.06	1.77±0.07	1.77±0.06	F3,105 = 2.01, p = 0.117	
BMI (kg/m^2) *Indeks telesne mase*	20.4±1.9	21.3±1.5	23.3±1.6	24.7±2.4	F3,105 = 30.13, p < 0.001	Q1,Q2<Q3<Q4
BF (%)/*Telesna masnoća*	11.7±1.2	14.2±0.6	16.6±0.8	20.7±2.0	F3,105 = 248.03, p < 0.001	Q1<Q2<Q3<Q4
SAR (cm)/*Sedi i dohvati*	23.1±7.1	23.9±6.7	24.0±7.2	21.9±5.4	F3,103 = 0.59, p = 0.623	
PWC170 (W · kg^{-1}) *Fizički radni kapacitet*	2.7±0.5	2.6±0.3	2.7±0.4	2.5±0.5	F3,104 = 1.64, p = 0.184	
Pmax (W · kg^{-1}) *Maksimalna snaga*	14.9±2.2	14.5±2.9	14.6±2.5	13.9±3.4	F3,98 = 0.52, p = 0.671	
Pmean (W · kg^{-1}) *Srednja snaga*	9.1±0.7	8.6±0.4	8.8±0.5	8.2±0.7	F3,98 = 8.37, p < 0.001	Q1,Q3>Q4
FI (%)/*Indeks umora*	37.7±6.9	42.6±8.8	43.1±8.3	44.5±7.7	F3,98 = 3.39, p = 0.021	Q1<Q4

BM body mass, Pmax maximal power, Pmean mean power, FI fatigue index and Q quartile group

(b) Physical working capacity at heart rate 170 beats/min (PWC170). PWC170 was performed according to Eurofit guidelines [16] on a cycle ergometer (828 Ergomedic, Monark, Sweden). Based on the linear relationship between heart rate and power output, PWC170 was calculated as the power corresponding to heart rate 170 beats/min and expressed as W/kg.

(c) Force-velocity test (F-v).The F-v test was employed to assess maximal anaerobic power (Pmax expressed as W/kg). This test employed various applied braking forces that elicit different pedaling velocities in order to derive Pmax [17]. The participants performed four sprints, each one lasting 7 sec, against incremental braking force (2, 3, 4 and 5 kg) on a cycle ergometer (Ergomedics 874, Monark, Sweden), interspersed by 5-min recovery periods.

(d) Wingate anaerobic test (WAnT). The WAnT [18] was performed on the same ergometer as the F-v did. Briefly, the participants were asked to pedal as fast as possible for 30 s against the braking force that was determined by the product of body mass in kg by 0.075. Mean power (Pmean), expressed in W/kg, was the main outcome of this test.

Statistical analyses were performed using IBM SPSS v.20.0 (SPSS, Chicago, USA). Data were expressed as mean and standard deviation. International cut-off points were employed to classify participants as normal, overweight or obese [19]. The association between physical fitness, BMI and BF was examined using Pearson's moment correlation coefficient (r). One-way analysis of variance (ANOVA) and Bonferroni post hoc test were employed to test differences in physical fitness between quartile groups of BMI and BF. Student t-test was used to examine differences between normal and overweight participants. The level of significance was set at α=0.05.

Results

Anthropometric and physiological characteristics of BMI and BF quartile groups are shown in **Table 1** and **2,** respectively. As demonstrated in these tables, there was an indication of decreased physical fitness in the highest quartile of BMI and BF. BMI was highly correlated with BF (r=0.70, p<0.001), fat mass (r=0.82, p<0.001), as well as with fat free mass (r=0.76, p<0.001), and BMI quartiles differed significantly with regard to their BF (F3,105=34.00, p<0.001). BMI could be predicted based on the equation BF=0.99·BMI–6.29 (standard error of estimate 2.54; **Figure 1**).

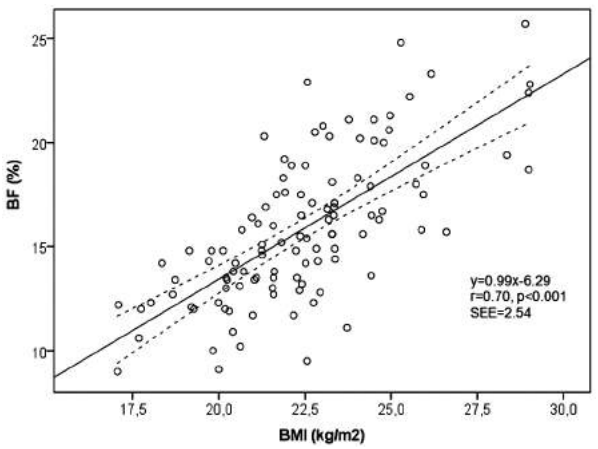

Fig. 1. Prediction of percentage of body fat from body mass index. SEE = standard error of estimate. Dashed lines represent 95% confidence intervals
Slika 1. *Predviđanje procenta telesne masnoće na osnovu indeksa telesne mase. SEE = standardna greška procene*

Table 3. Anthropometric and physiological characteristics of normal and overweight groups
Tabela 3. *Antropometrijske i fiziološke karakteristike grupa sa normalnom i prekomernom težinom*

	Normal (n = 89) *Normalna*	Overweight (n = 20) *Prekomenra*	t test
Age (yr)/*Starost (godine)*	17.1±0.5	16.9±0.5	t107 = 1.16, p = 0.249
BM (kg)/*Telesna masa*	66.4±7.0	80.7±9.6	t107 = -7.58, p < 0.001
Height (m)/*Visina*	1.76±0.06	1.75±0.07	t107 = 0.32, p = 0.748
BMI (kg/m^2)/*Indeks telesne mase*	21.5±1.7	26.2±1.7	t107 = -10.94, p < 0.001
BF (%)/*Telesna masnoća*	14.8±2.9	20.1±2.9	t107 = -7.26, p < 0.001
SAR (cm)/*Test 'sedi i dohvati'*	23.3±6.9	22.7±5.4	t105 = 0.38, p = 0.704
PWC170 ($W \cdot kg^{-1}$)/*Fizički radni kapacitet*	2.7±0.5	2.4±0.3	t106 = 2.06, p = 0.042
Pmax ($W \cdot kg^{-1}$)/*Maksimalna snaga*	14.3±2.6	15.1±3.3	t100 = -1.16, p = 0.250
Pmean ($W \cdot kg^{-1}$)/*Srednja snaga*	8.8±0.7	8.4±0.6	t100 = 2.34, p = 0.021
FI (%)/*Indeks umora*	41.9±8.4	42.6±7.9	t100 = -0.32, p = 0.747

BM - body mass, Pmax maximal power, Pmean mean power and FI fatigue index

BF was in inverse relationship with aerobic power (r=-0.21, p=0.029), maximal anaerobic power (r=-0.20, p=0.044) and local muscular endurance (r=-0.39, p<0.001), while the corresponding values of BMI were non-significant (r=-0.05, p=0.614; r=0.03, p=0.771; r=-0.12, p=0.220, respectively). However, both BF and BMI were directly related with fatigue index of Wingate anaerobic test (r=0.26, p=0.009; r=0.29, p=0.003, respectively). Non-significant correlations were found between flexibility and BMI (r=0.10, p=0.332) or BF (r=-0.11, p=0.256).

Based on international BMI cut-off points, 18.3% (n=20) of participants were classified as overweight and no one was obese. **Table 3** presents physical and physiological characteristics of normal and overweight participants, as well as their comparison. Some differences were revealed regarding aerobic power (PWC170) and certain aspects of anaerobic power (Pmean), with normal scoring better than overweight participants.

Discussion

The prevalence of overweight (18.3%) in our study was in agreement with findings in general population. For instance, a prevalence of 17.6% and 21.6% was previously reported in schoolchildren aged 11-17 years in France and Greece, respectively [20,21] and 23% in schoolchildren aged 16-19 years in Sweden [22]. Therefore, it is indicated that overweight affects young soccer players to a similar extent as it does general population. In contrast to general population, obesity was not recorded in our sample, which suggested soccer training as the effective means against adolescent BMI. The participation in a sport per se cannot guarantee that an adolescent is not overweight and proper family-, sport club-, and school-based exercise interventions should target weight and body fat control. The increase in body mass results from the misbalance between energy intake (nutrition) and energy expenditure (physical activity), and an optimal intervention should take into consideration both parameters, as well as genetic and environmental factors [20,23].

Even if the application of BMI in sport population has been questioned [8], it might be useful in youth soccer. Unlike sports, in which BMI could classify elite athletes as overweight or obese (e.g., American football [24]), soccer is a sport that is characterized by normal values of BMI (about 23 $kg \cdot m^{-2}$), as it has been shown by research in four elite European leagues [25]. In this context, the excess of body mass observed in our study was unexpected. Consequently, the elevated BMI of participants should not be attributed to sport-specific physiological adaptations. It is unlikely that the high BMI in our study is due to a healthy increase in muscle mass alone and it may not be without health consequences. The prevalence of overweight in our sample warrants further investigation to determine the health- and sport-related consequences of excessive weight in adolescent soccer players and to develop exercise intervention targeting weight management.

The results of this study indicate that BMI accounts for a large proportion of between-individual differences in BF; 49% of the variance in BF was explained by BMI. An important consideration was whether BF could be predicted from BMI in young soccer players. There was a close association between BMI and BF, and an acceptable standard error of estimate of the former based on the latter. On the other hand, BMI was similarly correlated with both fat mass and fat free mass. Therefore, our findings did not suggest further use of BMI as a measure of BF in soccer players aged 16-18 years. This correlation was comparable with findings in 5-19-year-old boys (r=0.79, p<0.001) [26]. It was also similar with what was found in Japanese general population aged 9-10 years (r=0.78, p<0.001) and 12-13 yr (r=0.79, p<0.001) [27], and higher than in the case of 4-11-year-old boys (r = 0.58, p<0.01) [9].

Based on previous studies on general population [10-13], it was hypothesized that there was an inverse relationship between BMI, BF and physical

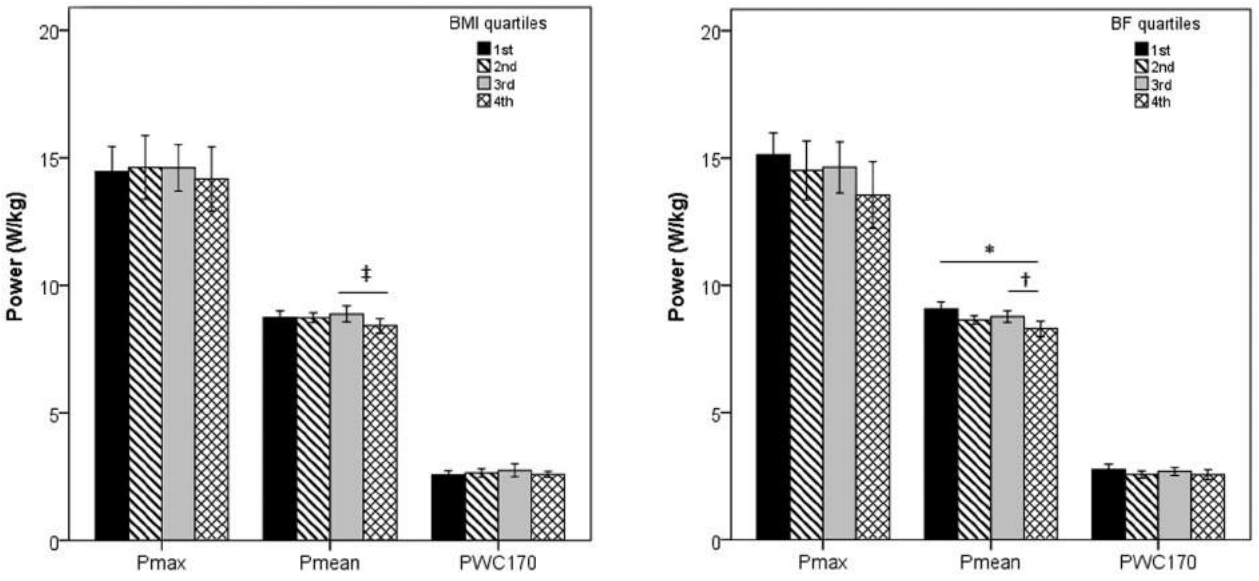

Fig. 2. Maximal anaerobic power (Pmax), estimated by a force-velocity test, mean power during Wingate anaerobic test (Pmean) and PWC170 for body mass index (left) and percentage of body fat quartile groups (right), ‡p<0.05, †p<0.01, *p<0.001

Slika 2*. Maksimalna anaerobna snaga, procenjena testom sila − brzina, srednja snaga za vreme Wingate anaerobnog testa i PWC170 za indeks telesne mase (levo) i procenat kvartilnih grupa telesne masnoće (desno), ‡p < 0,05, †p < 0,01, *p < 0,001*

fitness in soccer players. The negative values of the correlation coefficient between BF and physical fitness confirmed partially our hypothesis. BMI was significantly correlated with fatigue index (i.e., the decrease in performance during 30-s Wingate anaerobic test); the higher the BMI, the higher the decrease in performance. In addition to the correlation analysis, we examined differences between BMI and BF quartiles. The most interesting finding was derived from the comparison between BF quartiles (**Figure 2**), which revealed that the highest BF quartile scored lower in most of the tests. This suggests that a threshold does exist in BF, over which physical fitness is affected to a great extent.

The results emphasized the role of adiposity, but supported the role of BMI in youth soccer, as well. We found the association between mean power and fatigue index of Wingate test with BMI, in which the boys in higher BMI quartiles demonstrated reduced performance compared to those in lower quartiles. These associations were not similar for all the parameters of physical fitness that were examined. Flexibility was a parameter found to be in non-significant correlation with overweight and adiposity, which came to terms with previous observations [10].

The comparison between normal and overweight participants showed similar patterns as the comparison between BMI and BF quartile groups did (**Figure 3**). In spite of the fact that being overweight did not appear to be a limiting factor of short-term power output (Pmax), it exerted a negative effect on the cardiorespiratory power (PWC170) as well as on the capacity to maintain power during repeated actions (mean power, fatique index). Even though an important conceptual jump must be made when moving from laboratory findings to their practical implications, we can assume that overweight of a soccer player is a disadvantage with regard to maintenance of performance during the game or training.

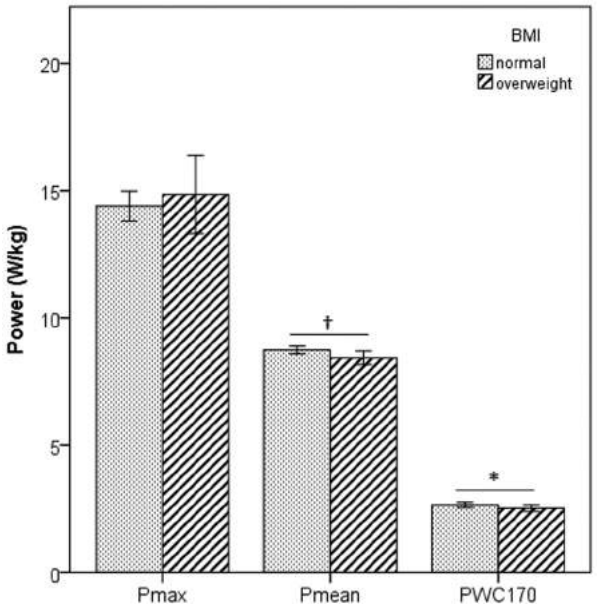

Fig. 3. Maximal anaerobic power (Pmax), estimated by a force-velocity test, mean power during Wingate anaerobic test (Pmean) and PWC170 for normal and overweight participants

Slika 3. *Maksimalna anaerobna snaga testom sila-brzina, srednja snaga za vreme Wingate anaerobnog testa i PWC170 za osobe sa normalnom i prekomernom težinom*

Conclusion

In conclusion, the prevalence of overweight among the participants was similar with what is observed in general population. Although none of the participants was obese, this finding highlights the excess of body mass in youth soccer as a novel concern for health and sport specialists. Except for flexibility, body fat was negatively associated with most of the physical fitness parameters under examination. These findings confirmed previous observations on general population about the negative effect of overweight on physical fitness.

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FRACTURE OF THE PATELLA AFTER THE ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

PRELOM ČAŠICE KOLENA POSLE REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA

Miroslav MILANKOV[1], Predrag RAŠOVIĆ[1], Nemanja KOVAČEV[1], Milan MILOVIĆ[2] i Veselin BOJAT[1]

Summary

Introduction. Fracture of the patella, after harvesting the central third of the patellar tendon for a bone–tendon–bone autograft, is a rare complication. **Material and Methods.** We made 1714 reconstructions of the anterior cruciate ligament of the knee using bone-patellar tendon-bone technique, and 7 patients had fracture of the patella (0.42%). The fracture was immediately recognized in the patients with vertical non-displaced patellar fracture and the broken screw osteosynthesis was carried out without changes in the rehabilitation period. One patient was treated non-operatively and patellar fracture in four patients was treated with operative reduction and osteosynthesis. **Results.** The patients were invited for the check-up 5 years (2-8 years) after surgery on average. The mean Lysholm score was 92 (85-100). All of them continued to engage in sporting activities at the same or greater level after 9 months on average (6-12 months). In all patients the Lachman test was with the firm stop compared to the other leg. X-ray changes in the patella were found in 2 patients who had multifragmentary fractures. **Discussion and Conclusion.** The fracture of patella can be prevented by avoiding to take too much bone graft, by using the most precise tools for cutting, while rehabilitation must be carefully planned. The optimal treatment of the fracture of the patella after the reconstruction of the anterior cruciate ligament is a firm osteosynthesis, which allows healing of the bone and continuation of the rehabilitation program.

Key words: Patella; Fractures, Bone; Anterior Cruciate Ligament Reconstruction; Arthroscopy; Postoperative Complications

Sažetak

Uvod: Prelom čašice kolena posle uzimanja kost-ligament čašice-kost kalema je retka komplikacija. **Materijal i metode:** Uradili smo 1 714 artroskopskih rekonstrukcija prednjeg ukrštenog ligamenta kost – ligamenet čašice – kost kalemom i kod sedam pacijenata je došlo do prelom čašice (0,42%). Kod pacijenta sa vertikalnim nedislokovanim intraoperativnim prelomom čašice, prelom je odmah prepoznat i izvršena je osteosinteza preloma zavrtnjem, bez promena u rehabilitacionom periodu. Jedan pacijent je lečen neoperativno dok je kod četiri pacijenta prelom čašice kolena lečen operativno krvavom repozicijom i osteosintezom. **Rezultat:** Pacijente smo pozvali na kontrolu prosečno 5 (2-8) godina posle operacije. Prosečan Lyscholm skor bio je 92 (85-100). Svi su nastavili da se bave sportskim aktivnostima na istom ili višem nivou. Kod svih pacijenata je Lachman test bio sa tvrdim zaustavljanjem u odnosu na drugu nogu. Radiografske promene su nađene kod 2 pacijenta sa višedelnim prelomima čašice. Povrtak sportskim aktivnostima bio je posle 9 (6–12) meseci. **Diskusija i zaključak:** U prevenciji ove komplikacije treba izbegavati uzimanje prevelikog koštanog kalema, koristiti što preciznije instrumente za sečenja, a rehabilitacija mora biti pažljivo dozirana. Optimalni tretman preloma čašice posle rekonstrukcije prednjeg ukštenog ligamenta kolena je čvrsta osteosinteza, čime se omogućava zarastanje kosti i nastavljanje rehabilitacionog programa.

Ključne reči: Patela; Frakture kosti; Rekonstrukcija prednjeg ukrštenog ligamenta; Artroskopija; Postoperativne komplikacije

Introduction

Bone-patellar tendon-bone (BTB) remains the most common graft material for anterior cruciate ligament (ACL) reconstruction, and has several advantages compared with soft tissue grafts. The BTB graft is the strongest of all biological substitutes; it achieves strong initial graft fixation using interference screws, and offers rapid bony integration at the fixation points of the reconstruction [1–4]. The results of its application are excellent in 80-90% cases with sporadic complications of the knee extensor mechanism, that is, BTB harvest site morbidity and disruption of the knee extensor apparatus [5,6]. Since 1983, when McCarrol [7] reported the first case of patella fracture that occurred 6 months postoperatively during a golf swing, few other authors have reported this complication [8–13].

The aim of this paper is to present the results of anterior cruciate ligament reconstruction in the patients in whom the intraoperative or postoperative fracture of the patella occurred and to show the underlying causes of these complications and possibilities of prevention.

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Abbreviations
ACL – anterior cruciate ligament
BTB – bone-patellar tendon-bone

Material and Methods

In the period from 1996 to 2011, 1714 reconstructions of the anterior cruciate knee ligament were done at the Department of Orthopaedic Surgery, Clinical Centre of Vojvodina using the BTB technique which was similar for all the patients. A vertical incision was made from the middle of the patella to the inferior portion of the tibia tubercle with the knee flexed. Skin flaps were created and the incision was sharply carried down through the transverse fibres of the paratenon. The paratenon was incised at its midpoint, and the scissors were then used to extend proximally and distally and to expose the entire width of the patellar tendon. Next, the tendon was maintained in a stretched position by flexing the knee to incise the tendon first on one side of the graft followed by the other side to yield a 10-mm wide graft. Then, a blade oscillating saw was used to create the tibial bone plug by scoring the tibial cortex and removing an equilateral triangle of bone with the saw. The tibial bone block was temporarily left in place while we harvested the patellar bone plug. We cut the patellar plug as a trapezoidal shape, no more than 6 or 7 mm deep, and then we used a curved osteotome to lift the tibial bone plug carefully from its bed onto a lap pad followed by gentle removal of the patellar bone plug. The scissors were then used to remove any remaining soft tissue attachments, and the graft was removed by the harvesting surgeon. The BTB graft was prepared on a side table by an assistant. A standard anterolateral portal was used as a viewing portal and an anteromedial one was used as a working portal. The ACL stump was debrided. In the period from 1996 to 2005 we created a femoral tunnel with a limited notchplasty using the TT technique. Since 2005, we have been making a femoral tunnel through the anteromedial portal. The femoral tunnel was created first in order to avoid excess fluid loss. The knee was placed in flexion between 110 and 120°. The femoral guide (Karl Storz, Tutlingen, Germany) with an appropriate offset was introduced into the joint through the anteromedial portal. With the help of a femoral guide, a drill-wire was placed into the centre of the anatomic insertion of the ACL at 10 o'clock position and was overdrilled with a 10-mm diameter reamer. A suture was retrieved and a guide pin was drilled into the joint followed by a cannulated reamer with an equal diameter to the graft to create the tibial tunnel. A grasper was then placed through the tibial tunnel to retrieve the suture. Then the graft was passed through the tibia into the femoral socket, and once the graft was properly positioned in the tunnel, it was fixed with RCI – round cannulated interference screws (Grujić & Грујић, Novi Sad, Serbia). Firm traction was applied to the tibial bone block while the full range of knee motion was being performed in order to pretense the graft and observe if the full extension caused any impingement. The graft was then tensioned using 60 N force (Karl Storz, Tutlingen, Germany) and fixed into the tibial tunnel with round cannulated interference screws (Grujić & Грујић, Novi Sad, Serbia). The knee stability was checked using Lachman and anterior drawer tests. Two drains were placed, the operative wound was closed in a usual way and the patient was taken to his room.

The patellar fracture occurred intraoperatively in two patients and postoperatively in 5 patients (0.42%) **(Table 1)**. There were two men and 5 women, their mean age being 23.5 years (19-30) and they went in for the following sports: basketball (1), soccer (1), karate (2), handball (1), recreational activities (2). The left knee was injured in 4 patients and the right knee in 3 patients. In 6 patients a fracture of the patella was on the same leg where there was the reconstruction of the anterior cruciate ligament in the knee, and on the second one from which the graft was taken from the opposite knee. The fracture developed in two cases intraoperatively; in one case seven days after surgery; in two cases after two months; and in two cases 7 months after anterior cruciate ligament reconstruction. We had to adjust the layout without dislocation in two patients; in three patients there was a two-part fracture and transversal; in another two it was multi-fragmentary. The fracture was immediately recognized in the patients with vertical non-displaced patellar fracture, and the broken screw osteosynthesis was carried out **(Figure 1AB)**, without changes in the rehabilitation period. One patient was treated non-operatively **(Figure 2ABC)** with plaster of Paris for 6 weeks which was followed by physical therapy **(Figure 3AB)**. In four patients patellar fracture was treated with operative reduction and osteosynthesis with needles and wire **(Figure 4AB)**.

The results were made based on the mean Lysholm score [14], arthrometric [15] and X-ray images.

Results

All patients were invited for the check-up 5 years after surgery on average (2-8 years). The mean Lysholm score was 92 (85-100). All of them have continued to engage in sporting activities at the same or greater level after 9 months on average (6-12 months). In all patients the Lachman test was with the firm stop, arthrometric 2 (1-3) mm compared to the other leg. X-ray changes in the patella were found in 2 patients, who had multi-fragmentary fractures.

Discussion

The use of patellar tendon autografts for ACL reconstruction is widespread and is deemed to provide good, reproducible clinical results [16]. Fracture of the patella, after harvesting the central

Table 1. Patients with knee patellar fracture after anterior cruciate ligament reconstruction using BTB autograph
Tabela 1. *Pacijenti sa prelomom čašice kolena posle rekonstrukcije prednjeg ukrštenog ligamenta korišćenjem autokalema "koštani deo čašice-ligament čašice-koštani deo golenjače"*

Case No *Pacijent broj*	1	2	3	4	5	6	7
Gender/*Pol*	Male/*Muški*	Female *Ženski*	Female *Ženski*	Male/*Muški*	Male/*Muški*	Male/*Muški*	Male/*Muški*
Age/*Starost*	19	22	18	23	29	30	24
Knee/*Koleno*	Left/*Levo*	Left/*Levo*	Left/*Levo*	Right/Desno	Right/Desno	Right/Desno	Left/*Levo*
Sporting activity *Sportska aktivnost*	Football *Fudbal*	Handball *Rukomet*	Handball *Rukomet*	Basketball *Košarka*	Recreational football *Rekretaivno fudbal*	Recreational fitness *Rekretaivno fudbal*	Karate *Karate*
Fractures after surgery *Nastank preloma posle operacije*	Intraoperatively *Intraoperativno*	7 days *7 dan*	7 months *7 meseci*	7 months *7 meseci*	2 months *2 mesec*	2 months *2 mesec*	Intraoperatively *Intraoperativno*
Type of fracture *Tip preloma*	Vertical *Vertiklani*	Transverse *Poprečni*	Transverse *Poprečni*	Transverse *Poprečni*	Multifragment *Višedelni*	Multifragment *Višedelni*	Vertical *Vetiklani*
Treatment *Lečenje*	-	Reposition and osteosynthesis *Repozicija i fiksacija*	Reposition and osteosynthesis *Repozicija i fiksacija*	Reposition and osteosynthesis *Repozicija i fiksacija*	Reposition and osteosynthesis *Repozicija i fiksacija*	Plaster immobilization *Gipsna imobilizacija*	Reposition and osteosynthesis *Repozicija i fiksacija*
Resume sport activities *Povratak sportu*	*6 meseci* 6 months	8 months *8 meseci*	12 months *12 meseci*	11 months *11 meseci*	10 months *10 meseci*	10 months *10 meseci*	6 months *6 meseci*
Lyscholm scor	100	85	96	90	84	87	100
Artrometar measurements in mm *Artrometarsko merenje u mm*	1	3	2	2	3	2	1
X-ray findings *RTG nalaz*	Repaired anatomically *Saniran anatomski*	Repaired anatomically *Saniran anatomski*	Repaired anatomically *Saniran anatomski*	Repaired anatomically *Saniran anatomski*	Reconstructed step 2 mm *Saniran stepenik 2 mm*	Reconstructed step 2 mm *Saniran stepenik 2 mm*	Repaired anatomically *Saniran anatomski*

third of the patellar tendon for a BTB autograft is a rare complication whose incidence ranges from 0.23% to 2.3% [9,13,17–19]. We made 1714 reconstructions of the anterior cruciate ligament of the knee using BTB technique, and had fracture of the patella in 7 patients (0.42%). In all but one patient the fracture was on the same side where the anterior cruciate reconstruction was done. In one case of the re-reconstruction of the ACL there was a fractured patella of the opposite knee from which graft was taken ten days after surgery.

The causes of patella fractures after anterior cruciate ligament reconstruction are manifold. First of all, taking a bone graft from the patella leads to a significant weakening of the bones **(Figure 1B)**. The recommendations for minimizing the risk of patella fracture include avoiding the use of osteotomes to make the initial bone cuts and to remove no more than 25 to 30 mm of the length of the patella, and no more than 9 to 10 mm of its width. The front part of the patella is the strongest and most resistant to the load, and its resistance after taking the graft [5] is reduced by 30%-40% without a significant increase in pressure between the patella and the femur [20,21]. Friis and al. [22], who investigated the biomechanical strength of the patella after taking the graft, found that the patella from which the graft was taken was more sensitive to stress than normal, and that the striped graft taken caused less stress on the bones than the oval or trapezoidal graft. The main conclusion of this study is that the lower part of the bone taken, the less stress on the patella, and the graft length should not exceed the

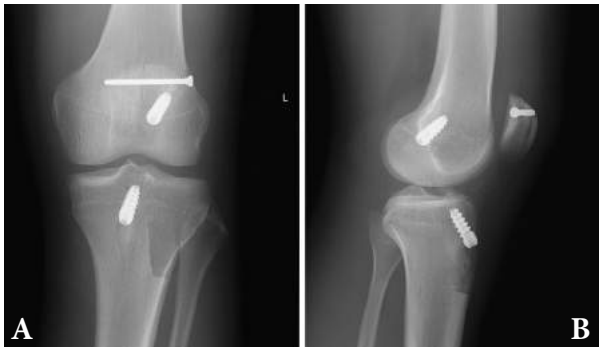

Fig. 1AB. Profile and AP radiograph of the left knee with patellar fracture occurred intraoperatively and immediately executed osteosynthesis with screw (Patient No. 7)
Slika 1AB. *Profilni i AP rendgenski snimak levog kolena sa intraoperativno nastalim prelomom čašice kolena i odmah izvršenom osteosintezom zavrtnjem. (Pacijent br. 7)*

equator of patella. Malek et al. [23] belive that the depth of the graft taken should not be more than one third of the patella thickness. Additionally, the technique of taking graft is critical. Osteotom should be used carefully after the initial cuts made by saw. Making a 45-degree angle to the upper pole of the graft during the intake may reduce postoperative stress. Jackson and al [24] propose the application of semi-circular oscillating saw with a smaller graft taken, and to form a smooth rounded bottom, which probably causes less stress than traditional methods in the angles.

McCarroll [1] presented the theory that the transverse patella fractures are similar to stress fractures due to reduced vascularization of the central parts of the patella. Benson and Barnett [25] described the patella vascularization and collateral blood flow after taking the graft. Extraossal blood supply surface of patella comes from geniculates artery that are stored while taking graft. The intraoosseous blood flow has three components: middle-patellar, polar and system from tendon and muscles quadriceps. The first two supply the middle third and lower pole of patella. If the damage occurs while taking graft, it can slow down the

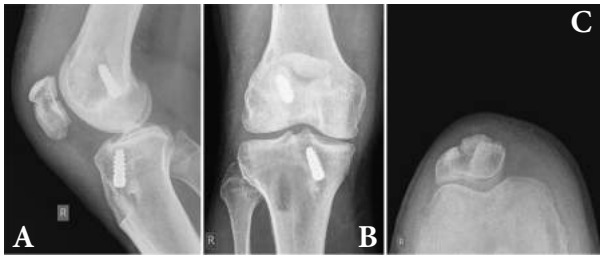

Fig. 2ABC. Profile, AP and tangentional radiograph of the knee, indicating the multifragment fracture of the patella. (Patient No. 6)
Slika 2ABC. *Profilni, AP i tangencionalni rendgenski snimak kolena na kome se vidi višedelni prelom čašice. (Pacijent br. 6)*

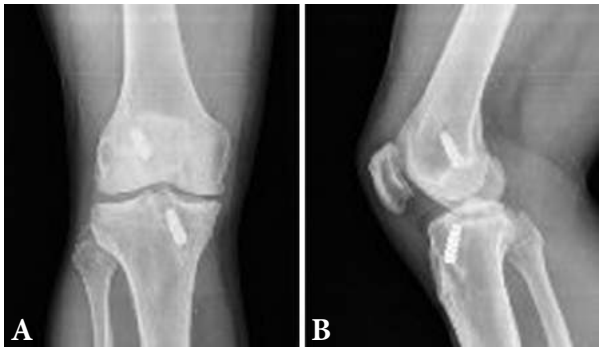

Fig. 3AB. Profile and AP radiograph of the patient No. 6 after two years. Fracture of the patella treated non-operatively, only with plaster immobilization, is repaired, but there are steps on the articular surface.
Slika 3AB. *Profilni i AP rendgenski snimak pacijenta broj 6 dve godine kasnije. Prelom čašice kolena lečen neoperativno gipsanom imoblizacijom je saniran ali postoji stepenica na artikularnoj površini.*

healing process on the graft, and affect the surrounding normal bone.

Bonami et al [6] studied the quality of tissue that filled the place where graft had been taken from during healing. A defect in the patellar ligament and patella filling fibrous tissue, which also reduces the strength and resistance of the anterior cortex of patella, predisposes fracture. Many authors [26-28] recommend filling the defect in the patella with spongious bone to preserve the anatomical integrity of the donor sites.

The majority of the described fractures happened during early postoperative period [8,25,29,30,31], an average of 57 days following BTB anterior cruciate ligament reconstruction, with an interval between 24 and 121 days. Christen et al. [9] described 6 intraoperative and 3 postoperative patella fractures in a series of 490 patellar autograft ACL reconstructions. Two of our patients sustained fractures of the patella,

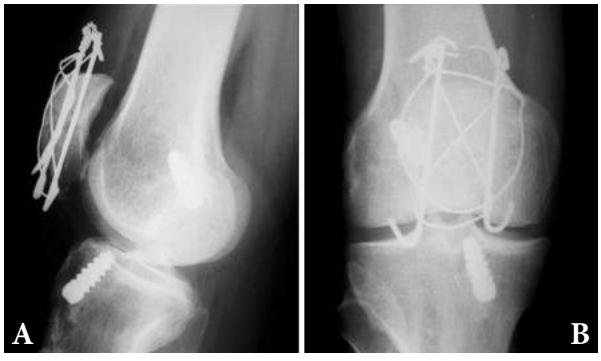

Fig. 4AB. Profile and AP radiograph of the knee after a bloody reposition and osteosynthesis patellar fracture (patient No. 5)
Slika 4AB. *Profilni i AP rendgenskio snimak kolena na posle krvave repozicije i osteosinteze preloma čašice (Pacijent br. 5)*

one after seven days, two after two months and two after 7 months, the average being78 days (0-210).

Intraoperative fracture of the patella occurred during bone block removal and usually vertical splits without dislocation. Out of 6 intraoperative fractures reported by Christen et al. [9], 3 were treated with internal fixation. In our first case we noted the existence of fracture without dislocation of the control X-ray that was made 6 weeks after surgery when the patient complained of constant pain in his patella. We slowed the rehabilitation program, and the fracture healed without affecting the final result. In another patient, a crack was heard and a non-displaced fracture of the longitudinal patella was noted after cutting the patella and lever strong chisels manipulation. We immediately made an osteosynthesis with one screw. The fracture healed without slowing down the rehabilitation program and it did not affect the final result.

Postoperative fractures occur with a direct blow results and impaction injury with the fracture being stellate or Y-shaped, while rapid eccentric quadriceps contraction, which may occur as the result of a fall, typically results in a transverse fracture pattern [32]. These fractures cause significant functional deficit that is manifested clinically as a loss of active knee extension. Rigid fixation to allow early mobilization is the recommended treatment for most isolated patella fractures [33] as well as for patella fractures in the postoperative period after ACL reconstruction. Non-operative treatment and treatments requiring extended immobilization should be reserved for those patients unwilling or unable to undergo surgery, or a fracture pattern that cannot be rigidly fixed. Once a patella fracture occurs, the short-term rehabilitation goals for the patient should be altered in order to enhance the likelihood of long-term success. Fracture healing without displacement is critical. There is a variety of fixation methods. Tension-band fixation has been reported with successful results [11]. However, as reported in the trauma literature, 22% of patients treated with tension-band wiring and early motion had displacement of more than 2 mm, and over 10% of patients will require hardware removal due to overlying irritation from the wire [34]. Other options include cannulated screw fixation, with or without a tension-band augment, or bicortical (superior to inferior) small or large fragment screw fixation. Biomechanical testing of a modified tension-band compared to either 4.5-mm screws or an anterior tension band placed through 4.0-mm cannulated screws showed the cannulated screws and tension band to be the strongest construction [35]. Regardless of the method selected, the surgeon must achieve reduction of the articular surface with stability throughout a range of motion. Once the fracture is reduced and stabilized, the knee must be taken through a range of motion to ensure no displacement is observed prior to closure. Postoperatively, the patient is allowed a protected progressive range of motion in a brace, but weight-bearing is allowed only in full extension. Hardware need not be routinely removed [36], but if symptomatic, it can be removed after the fracture has healed and ACL rehabilitation is complete.

The prevention of complications after reconstruction of anterior cruciate ligament rehabilitation has an important role. When postoperative quadriceps and hamstring muscles are impaired, they allow abnormal patellar mobility, which causes increased stress on the graft taken place. An early training of leg muscles with the return of neuromuscular proprioception is important for maintaining the knee stability and reducing the abnormal mobility of the patella [37].

The ways of avoiding an intraoperative patella fracture is to avoid larger bone plugs, minimize crosscuts that can act as stress risers, avoid deep cuts that might violate the articular surfaces, avoid levering the graft with osteotomes, and backfilling the defects with bone graft obtained at graft harvest or during tibial tunnel creation [38]. Postoperatively, it is important not to overload the patella in the first 6 to 8 weeks. Intraoperative fractures should be immediately treated with a firm osteosynthesis, and since they are usually without significant dislocations, they do not affect the rehabilitation process and the end result of ACL reconstruction. Fractures without dislocation are generally treated conservatively with immobilization; fractures with dislocation are treated by open reposition and internal fixation. Strong osteosynthesis allows early mobility and knee muscle exercises. The ultimate outcome of the reconstruction of the ACL does not change after post-operative fracture patella, it is the same as for an uncomplicated anterior cruciate ligament reconstruction of knee. If a patellar fracture occurs after the anterior cruciate ligament reconstruction, the best treatment is a firm osteosynthesis, which enables the healing of the bone, and immediate continuation of the previously resumed rehabilitation program. However, this complication prolongs the rehabilitation period and slows down the return to the sport field.

Conclusion

Patella fracture after anterior cruciate ligament reconstruction of the knee can be a serious problem in the total rehabilitation of the patient, and that possibility should be considered during anterior cruciate ligament reconstruction. These complications can be prevented by avoiding taking too much bone graft, by using the most precise tools for cutting, while rehabilitation must be carefully planned. After the reconstruction of the anterior cruciate ligament an optimal treatment of fractures of the patella is a firm osteosynthesis, which allows healing of the bone, continuation of the rehabilitation program and a good end result.

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BIRTH WEIGHT AND METABOLIC RISK IN WOMEN OF DIFFERENT NUTRITION LEVELS

TELESNA MASA NA ROĐENJU I METABOLIČKI RIZIK KOD ŽENA RAZLIČITIH KATEGORIJA UHRANJENOSTI

Mirjana MILOŠEVIĆ[1], Biljana SRDIĆ[1], Edita STOKIĆ[2], Marina RASTOVIĆ[3], Tatjana PAVLICA[4] and Radenko MATIĆ[5]

Summary

Introduction: Nowadays, obesity is one of the most important health problems in both developed and developing countries. Recent studies have shown a significant association of obesity and its complications with birth weight. The aim of our study was to analyze the effect of birth weight on the occurrence of metabolic disorders in normal weight and obese women. **Material and Methods:** The study group included 134 females of average age 41.71±11.56 years. In these women the relationship between birth weight and anthropometric and biochemical parameters, as well as with blood pressure values was analyzed. **Results:** Our results show that women with higher birth weight had higher values of the anthropometric indicators of fat mass and distribution (such as body mass index, total fat mass, waist circumference and hip circumference), as well as higher values of high density lipoprotein-cholesterol. In contrast, the values of systolic and diastolic blood pressure and low density lipoprotein-cholesterol were lower in women with higher birth weight. The analysis of metabolic profile in women of different nutritional status indicates that normal weight women with metabolic syndrome had a lower birth weight when compared with normal weight women without metabolic risk (3.15 *vs*. 3.40 kg, p>0.05). **Conclusion:** Higher birth weight is related with higher fat mass, while lower birth weight is related with metabolic disturbances. Birth weight seemed to be determinant of metabolic risk in normal weight women

Key words: Birth Weigh; Obesity; Risk Factors; Metabolic Syndrome X; Nutritional Status; Adult; Middle Aged; Female

Sažetak

Uvod: Gojaznost je jedan od najznačajnijih zdravstvenih problema današnjice sa kojim se suočavaju kako razvijene zemlje, tako i zemlje u razvoju. Dosadašnja ispitivanja su pokazala značajnu povezanost gojaznosti i njenih komplikacija sa telesnom masom na rođenju. Cilj našeg istraživanja bio je da se analizira uticaj telesne mase na rođenju na pojavu metaboličkih poremećaja kako kod normalno uhranjenih, tako i kod gojaznih žena. **Materijal i metode:** Ispitivanu grupu činile su je 134 osobe ženskog pola prosečne starosti 41,71±11,56 godina, kod kojih je analiziran odnos telesne mase na rođenju sa antropometrijskim i biohemijskim parametrima, kao i sa vrednostima krvnog pritiska. **Rezultati:** Naši rezultati ukazuju na veće vrednosti parametara mase i distribucije masnog tkiva (indeks telesne mase, ukupna masna masa, obim struka i obim kukova), kao i holesterola u lipoproteinima male gustine velike gustine kod osoba sa većom masom na rođenju. Suprotno, vrednosti sistolnog i dijastolnog krvnog pritiska, kao i holesterol u lipoproteinima male gustine padaju idući ka višim vrednostima mase na rođenju. Analizom metaboličkog rizika kod žena različitog stepena uhranjenosti uočava se da su normalno uhranjene žene sa rizičnim metaboličkim profilom imale niže vrednosti telesne mase na rođenju u poređenju sa normalno uhranjenim ženama bez metaboličkog rizika (3,15 *vs.* 3,40 kg, p>0,05). **Zaključak:** Osobe koje su imale veću telesnu masu na rođenju imale su veće vrednosti ukupne masne mase tela, dok je mala telesna masa na rođenju povezana sa metaboličkim poremećajima. Telesna masa na rođenju se pokazala mogućom determinantom metaboličkog rizika kod normalno uhranjenih osoba.

Ključne reči: Težina na rođenju; Gojaznost; Faktori rizika; Metabolički sindrom X; Nutritivni status; Odrasli; Srednje godine; Žensko

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Abbreviations

BMI	– body mass index
HDL	– high density lipoprotein
LDL	– low density lipoprtein
HOMA-IR	– insulin resistant index

Introduction

Nowadays, obesity is one of the major health problems in both developed and developing countries. The incidence of obesity reaches epidemic proportions - according to current data of the World Health Organization, more than one billion people are considered to be overweight, while 400 million people are considered to be obese [1-3]. The available data show that 54% of Serbian population are overweight, while in Vojvodina 35.5% of its population are overweight and 23% are obese [4]. Obesity is one of the most important risk factor not only for diseases such as type 2 diabetes and cardiovascular diseases, but also for some malignant diseases - breast, endometrial, prostate or colon cancer.

Epidemiological studies have shown a significant correlation between obesity and its complications and birth weight [5-8]. Research has shown that heart diseases cause death two to three times more often in people born with low birth weight than in those whose birth weight was higher than 4 kg [9]. It is believed that predisposition for the development of cardiometabolic disorders in adults is the result of adaptation of neuroendocrine mechanisms to poor energy supply during fetal development. Inadequate conditions and stress during prenatal period cause hypersensitivity of immune system, structural and functional changes of some organs and tissues – inadequate ratio between collagen and elastin increases tendency towards inflammation and vascular damage increases, that being the base for accelation of atherosclerosis [10,11].

On the other hand, higher birth weight is associated with the risk of developing obesity in later life [12,13]. However, it is still unknown which component of body composition is affected by birth weight and wheather it is a consequence of genetic predisposition or exclusively prenatal factors that caused higher birth weight.

Recent studies have shown that among normal-weight persons are those who are metabolically obese and that some overweight people are actually metabolically healthy [14,15]. The question is wheather these profiles are programmed during fetal life. Regarding this matter, the aim of our research was to analyze the effect of birth weight on the occurrence of metabolic disorders in normal-weight and obese women.

Material and Methods

The study group included 134 females of average age 41.71 ±11.56 years and different nutritional status. The participants underwent anthropometric measurements, their blood pressure was measured and the blood sample was taken for biochemical analyses. In addition, these women were asked about their birth weight.

The following anthropometric parameters were measured: body height, weight, waist circumference and hip circumference.

Body height was measured by Harpenden anthropometer (*Holtain Ltd, Croswell, UK*) with accuracy of 0.1 cm. Body weight was measured within the process of bioelectrical impedance measuring. Body mass index (BMI), calculated as the person's body mass in kilograms divided by the square of her height in meters, was used to estimate nutritional status. According to the recommendations of the World Health Organization, the participants having BMI of 18.5 to 24.9 kg/m^2 were considered to be normal-weight, those whose BMI was between 25 and 29.9 kg/m^2 were overweight and those whose BMI was higher than 30 kg/m^2 were obese [1]. Waist and hip circumference were measured by Holtain measurement tape (*Holtain Ltd, Croswell UK*) with an accuracy of 0.1 cm.

The standard equipment, *Riva-Rocci* sphygmomanometer, was used to measure systolic (SBP) and diastolic (DBP) blood pressure.

Glycaemia and parameters of lipid status were also analyzed and the values of insulinemia and insulin resistance index (HOMA-IR) were determined in 104 participants. Total cholesterol (HOL) and tryglicerides (TG) were determined by enzymatic procedures; whereas, HDL-cholesterol was determined by precipitation with sodium phosphotungstate and LDL-cholesterol by Friedwald's formula [16]. The values of fasting glucose were measured by *Diab glucosa GOD-PAP's* method. Enzyme immunoassay was used to determine serum insulin and insulin resistance, while insulin resistance was assessed by insulin resistance index: (glycaemia (mmol/L) x insulinemia (μU/mL))/22.5 [16].

Criteria of Karelis et al. were used to determine metabolic risk [17]. These criteria take into account the value of tryglicerides (<1.7 mmol/L), total cholesterol (<5.2 mmol/L), LDL-cholesterol (<2.6 mmol/L), HDL-cholesterol (>1.1 mmol/L) and HOMA-IR (<1.95). Those participants who met four of five criteria were labeled as metabolically healthy regardless of their nutritional status. Based on the assessment of metabolic risk the participants were divided into four groups: normal weight metabolically healthy, normal weight metabolically obese, obese but metabolically healthy and overweight with metabolic risk.

Software package *SPSS Statistics 17.0* was used for statistical analyses.

Results

Table 1 shows the descriptive characteristics of the study group. The participants were of different nutritional status (BMI values ranged from 17.86 to 59.30 kg/m^2) and of different type of fat distribu-

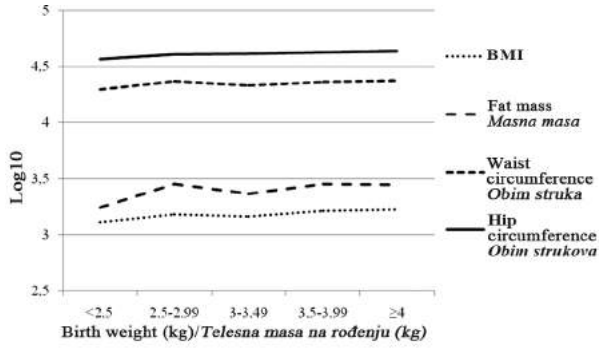
Table 1. Characteristics of the study group
Tabela 1. *Karakteristike ispitivane grupe*

	$\bar{X}$ ± SD	Min - Max
Age (years)/*Starost (godine)*	41.71 ± 11.56	20.00 – 76.00
Birth weight (kg)/*Telesna masa na rođenju (kg)*	3.34 ± 0.56	1.35 – 4.95
Body height (cm)/*Telesna visina (cm)*	165.11 ± 6.26	148.70 – 180.00
Body weight (kg)/*Telesna masa (kg)*	70.26 ± 18.77	45.00 – 170.00
BMI (kg/m^2)	25.85 ± 7.09	17.86 – 59.30
Fat mass (%)/*Masna masa (%)*	30.44 ± 8.28	9.10 – 55.40
Systolic blood pressure (mmHg)/*Sistolni krvni pritisak (mmHg)*	114.54 ± 17.26	90.00 – 180.00
Diastolic blood pressure (mmHg)/*Dijastolni krvni pritisak (mmHg)*	73.72 ± 9.91	50.00 – 100.00
Glycaemia (mmol/l)/*Glikemija (mmol/l)*	4.87 ± 1.59	3.30 – 19.70
Triglycerides (mmol/l)/*Trigliceridi (mmol/l)*	1.24 ± 1.41	0.46 – 12.53
Total cholesterol (mmol/l)/*Ukupni holesterol (mmol/l)*	5.58 ± 1.10	2.72 – 8.18
HDL-cholesterol (mmol/l)/*HDL-holesterol (mmol/l)*	1.53 ± 0.80	0.63 – 9.95
LDL-cholesterol (mmol/l)/*LDL-holesterol (mmol/l)*	3.59 ± 0.98	1.34 – 6.92
Waist circumference (cm)/*Obim struka (cm)*	81.17 ± 16.64	59.50 – 151.00
WSR	0.49 ± 0.10	0.35 – 0.90
Hip circumference (cm)/*Obim kukova (cm)*	102.73 ± 10.25	83.50 – 150.00
WHR	0.79 ± 0.10	0.66 – 1.21

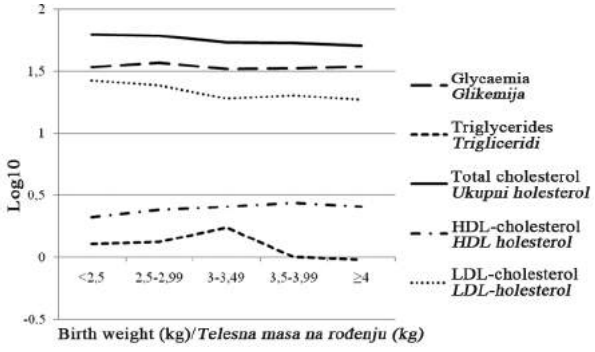
tion, and with different metabolic profiles (waist circumference was between 59 and 151 cm).

The subjects were afterwards divided into five categories based on their birth weight: <2.50 kg, 2.50-2.99 kg, 3.00-3.49 kg, 3.50-3.99 kg and ≥4.00 kg. The values of measured parameters in each category are shown in **Graphs 1, 2 and 3** (the values were first logarithmically transformed in order to improve the linearity). It is noticeable that the higher the birth weight, the higher the anthropometric indicators of fat mass and distribution as well as the values of HDL-cholesterol are. Thus, the average values of BMI and fat mass in women born with birth weight less than 2.5 kg were 22.56±3.14 kg/m^2 and 25.60±8.19%, respectively, while in those whose birth mass was over 4 kg they were 25.19±5.06 kg/m^2 and 31.38±8.34%. In contrast, the values of systolic and diastolic blood pressure and LDL-cholesterol were lower in women with higher birth weight. The average value of LDL-cholesterol in women with the lowest birth weight was 4.16±1.21 mmol/l, while in those whose birth weight was over 4 kg it was 3.55±0.99 mmol/l. However, the differences between the values of mentioned parameters in different categories of birth weight were not statistically significant.

The metabolic risk was estimated in 104 subjects whose value of HOMA-IR had been determined; they were then divided into four categories depending on the degree of their nutritional status and metabolic profile. The subjects with the metabolic risk profile had lower values of birth weight compared with those without the metabolic risk, but of the same nutritional status **(Table 2)**; whereby, a slightly larger difference was noticed among normal weight women (3.40±0.50



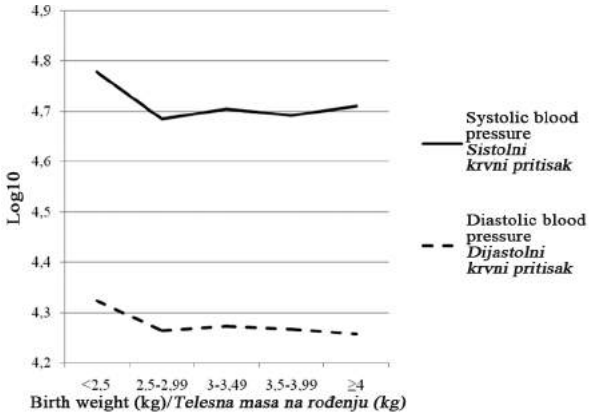
Graph 1. Values of anthropometric parameters in different categories of birth weight
Grafikon 1. *Vrednosti antropometrijskih parametara u različitim kategorijama telesne mase na rođenju*



Graph 2. Values of biochemical parameters in different categories of birth weight
Grafikon 2. *Vrednosti biohemijskih parametara u različitim kategorijama telesne mase na rođenju*

Table 2. Birth weight versus nutritional status and metabolic risk
Tabela 2. *Telesna masa na rođenju u odnosu na stepen uhranjenosti i metabolički rizik*

	Birth weight (kg)/*Telesna masa na rođenju (kg)*		
	$\bar{X}$ ± SD	Med (Min – Max)	ANOVA (Sig)
Normal weight/*Normalno uhranjene*			
Without metabolic risk/*Bez metaboličkog rizika*	3.40 ± 0.50	3.50 (2.30 – 4.60)	0.172
At metabolic risk/*Sa metaboličkim rizikom*	3.15 ± 0.66	3.25 (1.35 – 4.95)	
Obese/*Gojazne*			
Without metabolic risk/*Bez metaboličkog rizika*	3.47 ± 0.20	3.50 (3.25 – 3.65)	
At metabolic risk/*Sa metaboličkim rizikom*	3.42 ± 0.54	3.50 (1.80 – 4.50)	



Graph 3. Values of blood pressure in different categories of birth weight
Grafikon 3. *Vrednosti krvnog pritiska u različitim kategorijama telesne mase na rođenju*

vs. 3.15±0.66 kg). These differences, however, were not statistically significant.

Discussion

Numerous literature data suggest an association between low birth weight and risk for development of metabolic disorders, cardiovascular diseases, and even central deposition of adipose tissue in later life [18,19]. Conversely, higher birth weight is brought into connection with late onset of adiposity and lower risk of cardiovascular diseases and type 2 diabetes [18]. The aim of our research was to analyze the effect of birth weight on the occurrence of metabolic disorders in normal and obese women. The results indicate an association between higher birth weight and overweight in adulthood, as well as the probable impact of low birth weight on the development of metabolic risk profile in normal weight subjects.

It is shown that birth weight is positively correlated with body weight in later life. However, the data are heterogeneous with regard to influence of birth weight on body composition – a positive correlation is suggested both with fat and fat-mass [20]. Some authors assume that a higher cardiometabolic risk in subjects who had low birth weight resulted actually from their programmed lower fat-free mass [21], while others think that low birth weight predisposes central fat distribution [22]. Our findings suggest a closer relationship of birth weight to the size of fat component – persons with high birth weight had higher total fat mass than those with low or average birth weight.

Several studies indicate an association between low birth weight and high values of total cholesterol, fibrinogen and especially high values of blood pressure [23-27]. Huxley et al. [6] estimated that the reduction of birth weight by 1 kg led to an increase in systolic pressure by 2 do 5 mmHg. Eriksson et al. [9] found that people with lower birth weight were two to three times more likely to die from heart disease than those with higher birth weight. Our results also show that persons with low birth weight have higher values of systolic and diastolic pressure, total and LDL-cholesterol, and lower values of HDL-cholesterol in later life than people with higher birth weight. It is supposed that changes of adipose tissue play a key role in this and that after birth there is a sudden increase of adipose tissue with favoring its central deposition and modification of adipokine production (primarily, the reduction of adiponectin), thus contributing to the development of insulin resistance [18].

Recent studies have shown that the metabolic status is not directly dependent on the nutrition level and that obese people are not necessarily metabolically obese as well as that normal weight people could be metabolically obese. Data on the frequency of a healthy metabolic profile among obese people are heterogeneous – between 12.3% [17] and 51.3% [15], while the frequency of metabolic disorders among normal weight people, according to most studies, is less than 20% [28,29]. The data obtained for our population show that 14.35% of obese women have a healthy metabolic profile [30]. Bouchours-Nouet et al. [18] found that higher birth weight, followed by a rapid increase of body weight during the first two years of life, created the conditions for the development of protective mechanism for central obesity and insulin resistance, which could explain the occurrence of ”metabolically healthy obesity”, and that insulin resistance was related to the increase in body weight after the age of four. Salonen et al. [28] refer to the role of slow increase in body weight during the first seven years on the development of metabolic syndrome, while

Barker et al. [19] emphasize the effects of low birth weight on the development of insulin resistance only in people with high values of body mass index. Bearing in mind the association of low birth weight with metabolic risk profile, Ruderman et al. [14] included low birth weight in the screening system for detection of metabolic obesity in normal weight people. Conus et al. [29], however, found no significant differences in birth weight between normal weight women with and without metabolic obesity (3.13 *vs.* 3.15 kg). The difference in our study was slightly higher, although it was not statistically significant (3.15 *vs.* 3.40 kg) and shows a tendency to the development of a bit riskier metabolic profile in normal weight women with low birth weight. On the other hand, obese women at metabolic risk are insignificantly different in birth weight from those who are without the same risk.

A possible shortcoming of our study could be the fact that our sample was small, which may be the reason why there were no statistically significant differences. We were unable to obtain information about possible gestational diabetes in the participants' mothers that could contribute to greater homogeneity of the group by excluding its effect on birth weight. It is also necessary to mention that criteria for defining normal metabolic profile are not completely harmonized. We used the criteria set by Karelis and associates that take into account the values of total, HDL- and LDL-cholesterol, triglycerides and insulin resistance index. However, when evaluating metabolically healthy and obese people some studies use other criteria that include values of other parameters such as blood pressure, glycaemia or C-reactive protein. Their use might reveal some more aspects of the influence of birth weight on the cardiometabolic profile.

Conclusion

Based on these results we can conclude that women with low birth weight had higher values of systolic and diastolic pressure, total and low density lipoprotein-cholesterol and lower values of high density lipoprotein-cholesterol compared to women with higher birth weight. Moreover, people with higher birth weight had higher values of body mass index, total body fat mass as well as waist and hip circumference. Birth weight seemed to be determinant of metabolic risk in normal weight women.

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JOD I ŠTITASTA ŽLEZDA, SA NUKLEARNIM KATASTROFAMA I BEZ NJIH

IODINE AND THYROID GLAND WITH OR WITHOUT NUCLEAR CATASTROPHE

Ljiljana TODOROVIĆ ĐILAS, Ivana BAJKIN, Tijana IČIN, Jovanka NOVAKOVIĆ PARO i Branka KOVAČEV ZAVIŠIĆ

Sažetak

Uvod. Jod je mikroelement koji je neophodan i ograničavajući supstrat za sintezu hormona štitaste žlezde. On je esencijalni element koji omogućava štitastoj žlezdi da produkuje hormone tiroksin (T_4) i trijodotironin (T_3). *Sinteza hormona štitaste žlezde i metabolizam joda.* Tri molekula joda potrebna su za sintezu trijodtironina, a četiri molekula za sintezu tiroksina – dva ključna hormona koje proizvodi štitasta žlezda. *Deficit joda*. Za optimalnu funkciju štitaste žlezde važan je svakodnevni adekvatan unos joda. Kada je unos joda nedovoljan, smanjeno je stvaranje hormona štitaste žlezde, što može da uzrokuje hipotirozu, strumu i moždana oštećenja. Nedostatak joda je najčešći pojedinačni, preventabilni uzrok mentalne zaostalosti i moždanog oštećenja dece u svetu. Bolesti usled nedostatka joda oštećuju psihomotorički rast i razvoj i značajan su zdravstveni problem u svetu zbog posledica na fertilitet, natalitet i neonatalni mortalitet. *Prekomeran unos joda.* Na drugom kraju spektra je prekomeran unos joda koji je takođe udružen sa autoimunom bolesti štitaste žlezde i njenom disfunkcijom. *Upotreba joda u slučaju nuklearnih katastrofa.* U nuklearnim katastrofama (Hirošima, Nagasaki, Černobilj, Fokušima), zbog velike količine radioaktivnog joda, između ostalih teških posledica ozračivanja, došlo je do ogromnog porasta broja obolelih od karcinoma štitaste žlezde, posebno u dečjem uzrastu, te se u tekstu navode mogućnosti prevencije prema preporukama Svetske zdravstvene organizacije.

Ključne reči: Jod; Štitna žlezda; Tiroidni hormoni; Nesreće; Oslobađanje radioaktivnog materijala; Radioizotopi joda; Karcinomi štitne žlezde; Dete

Summary

Introduction. Iodine, as a trace element, is a necessary and limiting substrate for thyroid gland hormone synthesis. It is an essential element that enables the thyroid gland to produce thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). *Synthesis of Thyroid Hormones and Iodine Metabolism.* Three iodine molecules are added to make triiodothyronine, and four for thyroxine - the two key hormones produced by the thyroid gland. *Iodine deficiency.* The proper daily amount of iodine is required for optimal thyroid function. Iodine deficiency can cause hypothyroidism, developmental brain disorders and goiter. Iodine deficiency is the single most common cause of preventable mental retardation and brain damage in the world. It also decreases child survival, causes goiters, and impairs growth and development. Iodine deficiency disorders in pregnant women cause miscarriages, stillbirths, and other complications. Children with iodine deficiency disorders can grow up stunted, apathetic, mentally retarded, and incapable of normal movements, speech or hearing. *Excessive Iodine Intake.* Excessive iodine intake, which can trigger autoimmune thyroid disease and dysfunction, is on the other side. *Iodine use in Case of Nuclear Catastrophe.* In addition to other severe consuquences of radioactivity, high amount of radioactive iodine causes significant increase in incidence of thyroid gland carcinoma after some of the nuclear catastrophes (Hiroshima, Nagasaki, Chernobyl, Fukushima). The incidence of thyroid carcinoma was increased mostly in children. This paper was aimed at clarifying some of the possibilities of prevention according to the recommendations given by the World Health Organization.

Key words: Iodine; Thyroid Gland; Thyroid Hormones; Accidents; Radioactive Hazard Release; Iodine Radioisotopes; Thyroid Neoplasms; Child

Uvod

Jod je esencijalni mikroelement za sve žive vrste: nedostatak joda uvek oštećuje optimalnu funkciju štitaste žlezde, a dovoljan unos fizioloških potreba sprečava i/ili leči taj poremećaj [1]. Jod je integralni deo hormona štitaste žlezde trijodtironina (T_3) i tiroksina (T_4). Od ukupne količine joda u ljudskom organizmu preko 80% deponо-

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Skraćenice

T3	– trijodtironin
T4	– tiroksin
rT3	– reverzni trijodtironin
hTR	– humani receptor tiroidnog hormona
ATP	– adenozin-trifosfat
NIS	– natrijum/jod transporter
AIT	– apikalni jodni transporter
RaJ	– radioaktivni jod, radioactive iodine

vano je u štitastoj žlezdi vezano za specifični tiroidni glikoprotein – tireoglobulin [2,3].

Štitasta žlezda luči hormone: 3, 5, 3', 5'-tetrajodotironin (tiroksin, T_4) i 3, 5, 3'-trijodotironin (T_3) koji imaju značajnu ulogu u energetskom metabolizmu, tireokalcitonin (kalcitonin) koji ima ulogu u homeostazi kalcijuma i 3, 3' ,5' reverzni trijodotironin (rT_3), koji je posle rođenja biološki neaktivan [2]. Hormoni štitaste žlezde regulišu nivo i brzinu celulalnih metaboličkih procesa („okreću točak metabolizma''). Svoje brojne biološke uloge T_3 i T_4 ostvaruju vezivanjem na receptore u ćelijskom jedru (specifični nuklearni receptor − humani receptor tiroidnog hormona (hTR) - hTR-α, hTR-β) i mitohondrijama, čime direktno određuju aktivnost regulatornih gena. U ciljnim ćelijama proteaze odvajaju proteinski nosač od aktivnog dela hormona i većina T_4 dejodinira se u T_3 (T_4 je prohormon za T_3). Veza T_3 za receptor nekoliko puta je snažnija od veze receptor-T_4. Hormoni štitaste žlezde mogu da se vezuju na plazmatske i/ili mitohondrijalne membrane nezavisno od nuklearnih aktivnosti [3,4]. Efekti tiroidnih hormona ispoljavaju se praktično u svim tkivima i organima, od početka i u toku svake faze razvoja organizma [2−6].

Sinteza hormona štitaste žlezde, kao svaki proizvodni proces, zavisi od tri glavna elementa i počiva na njima: 1) dovoljno sirovina (JOD je limitirajući faktor, s obzirom da ga organizam ne može stvoriti, već samo uneti, pa je stoga esencijalan), 2) efikasnog proizvodnog procesa (složena enzimska kuplovanja) i 3) stalne kontrole kvaliteta (regulacija mehanizmima povratne sprege).

Sinteza tiroidnih hormona i metabolizam joda

Štitasta žlezda funkcioniše u složenom hipotalamo-hipofiznom okruženju [6]. Sinteza i sekrecija aktivnih tireohormona podrazumeva nekoliko sukcesivno povezanih procesa. Prvi je ulaz dovoljnih količina joda u štitastu žlezdu za izgradnju hormona. Jod se u štitastu žlezdu iz plazme transportuje aktivnim prenosom kroz bazalnu membranu tireocita, tzv. jodnom pumpom. Štitasta žlezda ima veliku sposobnost selektivne akumulacije jodida zbog čega je njegova koncentracija u žlezdi nekoliko desetina puta veća nego u plazmi. Odnos koncentracije jodida u plazmi i žlezdi je prosečno 25 : 1 (ali može da se poveća na 500 : 1 u određenim okolnostima), što je rezultat postojanja električnog gradijenta zasnovanog na tome da se unutrašnjost tirocita ponaša kao električno negativno polje u odnosu na okolni intersticijum [2,5,6]. Jod u štitastu žlezdu ulazi u obliku anorganskog jodida ili jonskog joda poreklom iz gastrointenstinalnog trakta (jodidi uneti hranom, vodom, jodiranim agensima i/ili lekovima) ili oslobađanjem posle dejodinacije tireoglobulina. Najveći deo joda iz hrane, pre apsorpcije u tankom crevu redukuje se u neorganski jodid i kao takav vrlo brzo i skoro potpuno resorbuje [5]. Jodirane aminokiseline, T_4 i T_3 transportuju se nepromenjene kroz crevni zid, kao i kratki jodopeptidi koji se mogu resorbovati bez prethodne proteolize [3,5]. Jodni kontrasti koji se koriste u radiografiji apsorbuju se nepromenjeni u crevu, a kasnije se odvaja jod. Plazmatska koncentracija jodida obično je ispod 10 μg/l. Najveću količinu jodida iz plazme uklanjaju štitasta žlezda i bubrezi, zanemarljivo male količine joda izlučuju se pljuvačkom i stolicom.

Količina joda koju štitasta žlezda preuzima iz plazme je manje-više konstantna − kada neorganski jod u plazmi opada, tiroidni klirens raste. Tiroidni klirens joda može da se poveća i do 100 ml/min u stanjima jodnog deficita ili da padne na 3−4 ml/min kada postoji hroničan dnevni unos joda 500−600 μg/dan [5,7]. Male, ali detektabilne količine joda prisutne su u salivi i u ekspiratornom vazduhu. Mlečne žlezde u periodu laktacije, slično štitastoj žlezdi, koncentrišu velike količine joda iz plazme, najviše u toku prva 24 sata posle ingestije [5,8]. Koncentracija joda u humanom mleku direktno zavisi od dnevnog unosa joda ishranom [4,5,8].

Prirodni izvori joda su uglavnom riba i plodovi mora, dok su u ostalim namirnicama količine minimalne. Dodatni izvori joda, često i uzroci predoziranosti jodom su neki medikamenti, amiodaron, povidon jod, jodna kontrastna sredstva u radiologiji.

Prve akcije jodiranja soli sprovedene su 1922. godine u Švajcarskoj, 1924. u SAD, Austriji i Bavarskoj. U našoj zemlji je sredinom prošlog veka, uredbom od 1953. godine, uvedeno obavezno jodiranje kuhinjske soli. Godine 1948. koncentracija KJ u soli bila je 5 mg KJ/kg NaCl, 1955. godine 10 mg KJ/kg NaCl, a danas se vrši sa 20 mg KJ na 1 kg soli, čime je izvršena prevencija jodnog deficita i njegovih posledica − pre svega gušavosti, kretenizma itd. [9]. Akcija jodiranja soli započela je zaslugom prof. dr M. Kičića. Ovom uredbom naša zemlja se svrstala u red jedne od prvih zemalja u Evropi koje su postigle eradikaciju endemske gušavosti i jodnog deficita.

Preuzimanje joda u štitastu žlezdu

Normalno je da je plazmatska koncentracija joda višestruko niža u poređenju sa intratirocitnom, pa se aktivan transport i koncentrisanje joda u štitastoj žlezdi obavlja uz utrošak energije i O_2 za aktivnost plazma-membranske Na^+-K^+, ATP-aze osetljive (senzitivne) na quabain [3,10]. Aktivan prenos

Tabela 1. *Preporučeni dnevni unos joda prema Svetskoj zdravstvenoj organizaciji*
Table 1. *World Health Organization recommendations for iodine intake amounts*

Uzrast/*Age*		Jod - dnevne potrebe (μg/dan) *Iodine intake (μg/day)*
Odojče	0-6 meseci/0-6 *months*	40
Infants	6-12 meseci/6-12 *months*	50
Deca	1-3 godine/1-3 *years*	70
Children	4-6 godina/4-6 *years*	90
	7-10 godina/7-10 *years*	120
Dečaci i devojčice/*Adolescents*	11-18 godina/11-18 *years*	150
Odrasli/*Adults*	> 19 godina/> 19 *years*	150
Trudnice/*Pregnant women*		175
Dojilje/*Breastfeeding women*		200

joda vrši transportni protein u bazolateralnoj membrani tireocita, Na/J simporter (NIS). Ovo je energetski vezana hemijska reakcija – transmembranski se istovremeno prenose 2 jona Na^+ (u korist elektrohemijskog gradijenta) sa jednim atomom joda (nasuprot elektrohemijskog gradijenta) **(Slika 1)**.

Dopremanje joda u lumen folikula je dvostepeni transport: aktivni prenos kroz bazolateralnu membranu tirocita NIS simporterom i pasivan transport kroz apikalnu plazmatsku membranu. Drugi transportni korak obavlja transportni protein pendrin [5,11] i apikalni jodni transporter (AIT, *Apical Iodide Transporter* [11].

Količina joda ima snažne efekte na produkciju tirohormona [5,7,12,13]. Svaka faza složenih biohemijskih procesa od sinteze tiroksina i trijodtironina do ostvarivanja njihovih bioloških efekata može biti blokirana. Adekvatna količina bioraspoloživog joda neophodna je za normalnu funkciju štitaste žlezde. Oštećenje funkcije jednako nastaje pri hroničnom jodnom deficitu i kod velikog priliva jodida [1,7,13,14]. Grafički ovo može da se prikaže kao dozno-zavisna kriva funkcionalnog odgovora na količinu oligoelementa **(Slika 2)**. Osenčena površina predstavlja disfunkcionalnost na oba kraja spektra, čak smrt ćelije, jednako potentnu u deficitu i u obilju joda.

Sam jod i jodotirozini u višku ili u promenjenom međusobnom odnosu, ali i druge jodirane materije (npr. albumin ili jodolipidi, posebno 2-jodoheksadekanal koji nastaje u štitastoj žlezdi posle administracije KJ i njegova koncentracija povećava se linearno sa daljim dodavanjem joda), mogu da inhibiraju sintezu i sekreciju tirohormona. Inhibicijom enzimske aktivnosti nikolinamid-adenit-dinukleotid fosfat (NADPH) oksidaze remeti se produkcija H_2O_2 i na taj način sprečava jodinacija tireoglobulina [15–17]. Pretpostavlja se da je ovo najodgovorniji biohemijski mehanizam kojim jod u suvišku blokira tiroidnu hormogenezu –Volf-Čajkofov (*Wolff-Chaikoff*) efekat [18]. Preporučeni dnevni unos joda prema Svetskoj zdravstvenoj organizaciji dati su u **Tabeli 1**.

Kontrola unosa joda u jednoj sredini može se uraditi jedino merenjem dnevne eliminacije joda, odnosno merenjem jodurije. Postoje takođe kriterijumi Svetske zdravstvene organizacije po kojima je u području bez endemije jodurija 60–100, blaga endemija 50, umerena endemija 25–50 i teška endemija 25 μg joda za 24 h.

Deficit joda

Adaptacija na nedostatak joda nije ispoljena samo povećanjem plazmatskog klirensa joda. Generalno, adaptacijski mehanizmi na nedostatak joda usmereni su na bolje konzerviranje i efikasniju bioiskoristljivost limitiranog esencijalnog resursa [19].

Bolesti nastale zbog nedostatka joda

Nedostatak joda može ozbiljno da ošteti zdravlje u svakom životnom dobu. Zavisno od razvojnog perioda, vremena trajanja i veličine jodnog deficita ispoljavaju se bolesti usled nedostatka joda (*engl. Iodid Defficiency Disorders, IDD*) **(Tabela 2)**.

Jodni eksces

Pored adaptivnih mehanizama na nedovoljan unos joda, postoje zaštitni mehanizmi štitaste žlezde i od prekomernog unosa joda. Najčešći uzrok povećanog priliva joda u mnogim zemljama su farmakološki preparati **(Tabela 3),** a u drugim zamljama − na primer u Japanu, prehrambene namirnice npr. plodovi mora, naročito alge (kelp) [5,12,15,20,21].

Posledice jodnog ekscesa mogu biti: Volf-Čajkofov efekat, hipotiroidizam, struma, hipertiroidizam, Bezedovljeva bolest, struma (*Jod-Basedowi, struma Basedowificata*), autoimune tiroidne bolesti, karcinom štitaste žlezde [22–25].

Primena joda u slučaju nuklearnih katastrofa

Od kada postoje nuklearne elektrane, nuklearne nesreće dešavaju se povremeno. Događaji ozbiljnih razmera su ređi, ali daleko katastrofalniji. Internacionalna agencija za atomsku energiju (*International Atomic Energy Agency IAEA*) napravila je skalu težine nuklerne nesreće od 1 do 7

Tabela 2. *Spektar bolesti nedostatka joda*
Table 2. *Iodine deficiency disease spectrum*

Fetus *Fetus*	Pobačaj/*Abortion* Prevremeno rađanje/*Preterm birth* Povećana smrtnost pri porođaju/*Increased newborn mortality* Urođene mane/*Congenital disorders* Kretenizam/*Cretinism* Gluvonemost/*Deaf-mute disorders*
Novorođenče *Newborn*	Novorođenačka gušavost/*Newborn goiter* Hipotiroidizam/*Hypothyroidism* Umna zaostalost/*Mental retardation* Povećana osetljivost štitaste žlezde na štetan uticaj radioaktivnih materija *Increased susceptibility of thyroid to radioactive damage*
Deca i adolescenti *Children and adolescents*	Gušavost/*Goiter* Hipotirodizam ili hipertiroidizam/*Hypothyroidism or hyperthyroidism* Smanjene intelektualne sposobnosti/*Decrease in cognitive function* Fizička zaostalost (nizak rast, nepostojanje polnog razvoja, koštano-zglobni deformiteti) *Physical retardation (growth disorders, sex development disorders, bone and joint deformities)* Povećana osetljivost štitaste žlezde na štetan uticaj radioaktivnih materija *Increased susceptibility of thyroid to radioactive damage*
Odrasli *Adults*	Gušavost/*Goiter* Hipotirodizam ili hipertiroidizam/*Hypothyroidism or hyperthyroidism* Smanjene intelektualne sposobnosti/*Decrease in cognitive function* Povećana osetljivost štitaste žlezde na štetan uticaj radioaktivnih materija *Increased susceptibility of thyroid to radioactive damage*

[26]. Nuklearne nesreće težine 4–7 bile su: Harisburg 1979. godine, Černobilj 1986, Fokušima 2011. godine. Černobilj i Fokušima bile su nesreće 7. stepena. Fokušima je posledica prirodne katastrofe, dok su ostale nastale kao posledica ljudske greške. Postoje uputstva za ponašanje u slučaju nuklearne katastrofe, međutim, dobro bi bilo imati i jednostavna uputstva za opštu populaciju i time bi se izbeglo neadekvatno ponašanje. Na primer, neke apoteke u Evropi su rasprodale sve tablete joda posle Fokušime, a da u Evropi posle ove katastrofe profilaksa jodom nije preporučena.

Biološka distribucija RaJ unetog u organizam odvija se na način kao i distribucija običnog joda. Dolazi do resorpcije u gornjim delovima tankog creva; u cirkulaciji se vezuje za proteine; akumulira se u štitastoj žlezdi; eliminacija je putem bubrega gde se reapsorbuje 75% u distalnim tubulima. Ima vrlo kratak poluživot od 0,43 dana, dok se oko 60% unetog RaJ zadržava duže. Poluživot je oko 7,61 dana (urin, pljuvačka, znoj). Radioaktivno obeleženi jod, J131, J128 po istom mehanizmu nakon ulaska u organizam najvećim delom se ugrađuje u štitastu žlezdu i tu deluje direktno na jonizaciju tiroidnog tkiva, nekrozu tirocita, podstiče proliferaciju, stvaranje pseudolobulusa, a time moguće i malignu alteraciju i proliferaciju. Nakon zabeleženih nuklearnih katastrofa opisano je hiljade dece obolele od tiroidnog karcinoma. Rizik od karcinoma štitaste žlezde zavisi od doze radijacije [19,27].

Većina karcinoma štitaste žlezde posle Černobilja javila se kod dece mlađe od 6 godina u radijusu od 100 km od elektrane. Preko 5 000 dece i adoescenata do 18 godina na teritoriji u blizini elektrane u vreme katastrofe dobilo je karcinom štitaste žlezde. Većina je preživela, ali nakon operacije moraju da žive bez štitaste žlezde, sa doživotnom supstitucijom i doživotnim praćanjem. Čak i kratkotrajna izloženost radioaktivnom jodu može da dovede do mutacija u žlezdi i povećanja rizika od karcinoma. Zabeležena je i povećana incidencija leukemija među radnicima koji su bili jako ozračeni. Takođe je primećena povećana stopa karcinoma dojke u Belorusiji 2,2 puta i u Ukrajini 1,4 puta, 10–15 godina nakon izlaganja radioaktivnom jodu kod žena starosti 45 godina. Humano tkivo dojke preuzima male količine joda (dokazano postojanje NIS u tkivu dojke) [28]. U svim starosnim grupama, od novorođenačkog doba do starosti, pri nedostatku joda postoji povećana osetljivost žlezde na štetan uticaj radioaktivnih materija. Jedina moguća prevencija vezivanja radioaktivnog joda je pravovremena saturacija organizma običnim elementarnim jodom. Nacionalne zdravstvene ustanove procenjuju rizik i preporučuju na kojoj teritoriji i kada je neophodno primeniti tablete joda [29].

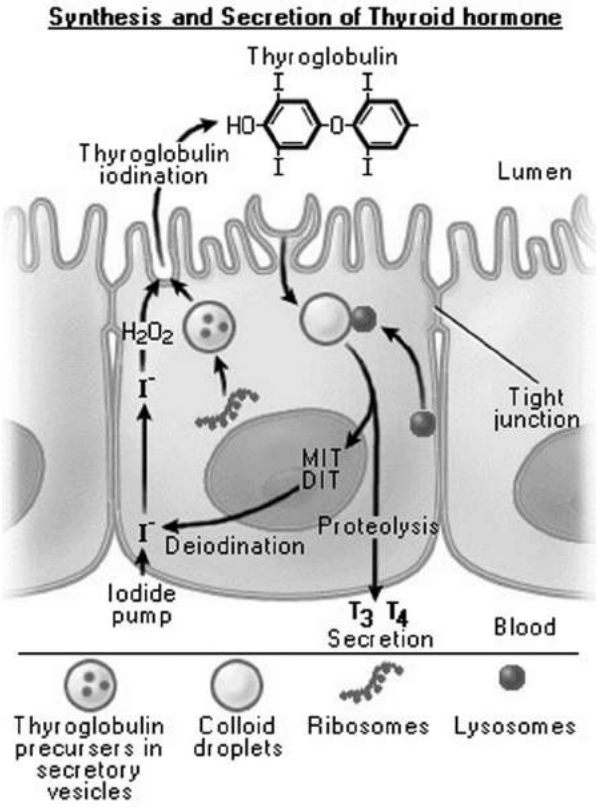
Kalijum-jodid je isti oblik joda koji se primenjuje za jodiranje kuhinjske soli. Dat u dovoljnoj količini, zasiti štitastu žlezdu stabilnim jodom i tako sprečava preuzimanje radioaktivnog joda u žlezdu u slučaju nuklearne katastrofe. Postoji u tečnom obliku i u obliku tablete. Pravilno zapakovane tablete imaju dugi vek trajanja i do 5 godina, a ukoliko se uzmu one tablete sa isteklim rokom, neće delovati u potpunosti ali neće imati štetnih efekata. Ovaj preparat joda štiti tiroidnu žlezdu od svih izvora RaJ: vazduh, voda, hrana, mleko. Uvek se poseb-

Tabela 3. *Sadržaj joda u različitim farmakološkim preparatima*
Table 3. *Iodine concentration in different drugs*

Zasićeni rastvor kalijum-jodida/*Potassium iodide solution*	18 mg/kapsula/*18 mg per capsule*
Lugolov rastvor/*Lugol's solution*	6 mg/kapsula/*6 mg per capsule*
Amiodaron (200 mg)/*Amiodarone (200 mg)*	75 mg/tableta/*75 mg per tablet*
Povidon jod (ml)/*Povidone iodine (ml)*	10 mg/ml/*10 mg/ml*
Ipodat, iopanoat (kapsula)/*Ipodat, iopanoat (capsules)*	308 i 350 mg/kapsula/*308 or 350 mg per capsule*

no ističe da u kontaminiranim područjima treba izbegavati mlečne proizvode [27,30,31].

Posle nesreće u černobiljskom nuklearnom reaktoru, Poljska je uspešno prevenirala pojavu karcinoma kod svog stanovništva, tako što je svima dat KJ čim se pojavila vest o nesreći. Ovo nije bio slučaj u bivšem Sovjetskom Savezu gde se kod 1 800 dece u ugroženom regionu razvio tiroidni karcinom, a kod još hiljade njih se razvio tiroidni karcinom godinama kasnije. Samo zdravstvene vlasti mogu da utvrde koji radioaktivni izotopi su oslobođeni, da li je tu i RaJ, kada da se krene sa tabletama KJ i koliko dugo. Takođe je značajno da zdravstvene institucije daju uputstva bez zakašnjenja. Poljska je pravi primer pravovremeno datog uputstva nakon Černobilja [32, 33]. U Finskoj, gde se akcije nakon katastrofa obično preduzimaju odmah, ovoga puta prva informacija dobijena je sa Švedskog radija kada je nuklearni otpad već prešao preko Finske u Švedsku.



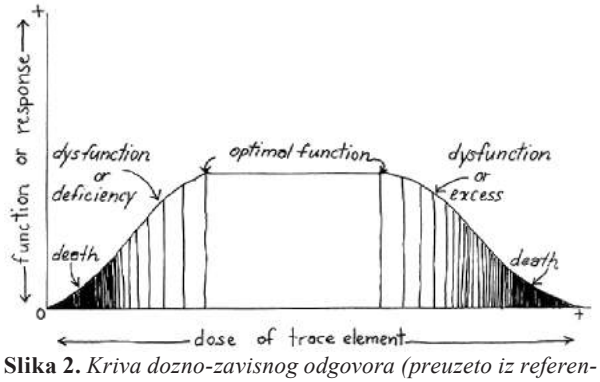
Slika 1. *Shema prenosa joda NIS simporterom*
Fig. 1. *Scheme of NIS symporter iodine transport*

Ne znači i svako ispuštanje radioaktivnog materijala i ispuštanje RaJ, koji može izazvati karcinom štitaste žlezde. Na primer „prljava bomba" ne mora sadržati RaJ, s obzirom na njegov jako kratak poluživot. To je konvencionalna bomba sa radioaktivnim materijalom, dizajniranim da eksplodira i tako raspe radioaktivne izotope i zagadi što šire područje. U ovakvim okolnostima tablete KJ nisu potrebne. Potrebno ga je uzeti 6–12 sati pre izlaganja RaJ, a deluje protektivno i ako se uzme u prvih nekoliko sati nakon izlaganja RaJ. Trebalo bi uzimati jednu dozu na dan dok traje ekspozicija i jedan dan nakon prestanka izloženosti RaJ. Zdravstvene vlasti su dužne da utvrde koji je radioaktivni izotop oslobođen, kada da se krene sa KJ i koliko dugo da se uzima [27,30,31].

US Food and Drug Administration − FDA izdala je preporuke za minimalne doze KJ: 130 mg KJ za odrasle, 65 mg KJ za decu 3–18 godina, 32 mg KJ za decu od 1 meseca do 3 godine i 16 mg KJ za bebe do 1 meseca.

U Americi se tablete prodaju u dozama od 130 i 65 mg, perforirane su radi lakšeg doziranja, a za malu decu se tope u vodi. *Nuclear regulatory Commission* obavestila je države da postoje besplatne zalihe KJ na zahtev.

Jod ne treba dati osobama koje nemaju štitastu žlezdu (stanje posle ablacija, hirurške ili terapijske doze RaJ u okviru lečenje hipertireoidizma). Takođe jod ne treba dati osobama sa alergijom na jodne preparate, tiroidnom bolešću, herpetiformnim dermatitisom (kožni oblik celijačne bolesti), određenim tipovima vaskulitisa. Gravidne žene bi trebalo da uzimaju istu dozu kao i odrasli, uz poseban oprez u drugom i



Slika 2. *Kriva dozno-zavisnog odgovora (preuzeto iz reference 13. sa dozvolom)*
Fig. 2. *Dose-dependent response curve (reference no 13 with permission*

trećem trimestru graviditeta, kada je već formirana štitasta žlezda, jer s obzirom da jod prolazi kroz placentu, postoji mogućnost blokiranja fetalne tiroidne žlezde, posebno u područjima sa jodnim defictom [34].

Zaključak

Prevelik unos joda povećava učestalost hipertiroze indukovane jodom, autoimunih tiroidnih bolesti i eventualno tiroidnog karcinoma.

Premalo unosa joda uzrokuje mentalnu retardaciju, strumu, hipotirozu i druge takozvane bolesti nedostatka joda.

Svetska kampanja u borbi za iskorenjivanje bolesti usled nedostatka joda obasjala je novim svetlom značaj joda i oštećenja zdravlja koja mogu da se razviju kada postoji nedostatak joda, ali i njegov preteran unos.

U našoj zemlji ne postoji nacionalni registar obolevanja od štitaste žlezde i nema aktuelnih podataka o stanju ishranjenosti stanovništva jodom.

Praćenje jodurije kao pokazatelja jodnog deficita najčešće se rutinski ne radi, te bi to bilo neophodno bar za rizične kategorije, dece i trudnica.

Edukacija o značaju joda za ljudsko zdravlje i postojanje nacionalnog registra tiroidne patologije značajno bi koristilo u planiranju i sprovođenju redovnih skrininga na tiroidna oboljenja, posebno kod dela populacije izloženog riziku.

U slučaju nuklearnih katastrofa neophodno je preduzeti tačne korake za prevenciju tiroidnog karcinoma. Neophodno je da državne zdravstvene institucije daju pravovremena uputstva o stepenu i vrsti ozračenosti, kao i postupku preventivnog davanja kalijum-jodida prema važećim preporukama. Država bi morala imati rezerve kalijum-jodida koje bi besplatno delila u predviđenjim dozama.

Neophodno je u svakoj situaciji sačuvati zdrav razum, zatim slušati preporuke koje su dale nadležne zdravstvene institucije i postupiti prema njima.

Nadamo se da će čovek, zahvaljujući napretku nauke, pronaći manje opasne izvore energije od nuklearnih elektrana i da ćemo pokušati da sprečimo zagađenje nuklearnim otpadom.

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PERINATALNA TUBERKULOZA − PRISTUP DIJAGNOSTICI I TERAPIJI

PERINATAL TUBERCULOSIS – DIAGNOSTIC AND THERAPEUTIC APPROACH

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Sažetak

Uvod. Unazad trideset godina beleži se porast obolelih od tuberkuloze. Klasični trend obolevanja u pojedinim dobnim grupama se takođe menja. Epidemiološki podaci ukazuju na to da je došlo do porasta broja trudnica sa tuberkulozom što utiče na incidenciju perinatalane tuberkuloze. *Trudnoća i tuberkuloza.* Klinička slika tuberkuloze u trudnoći je varijabilna. Efekat tuberkuloze na trudnoću zavisi od raznih faktora: mesta i forme bolesti, ishranjenosti, imunostatusa majke i konkomitantnih bolesti majke, stadijuma trudnoće u kome je započeto lečenje i dr. Često se klinički simptomi ispolje kod već razvijene forme perinatalne tuberkuloze, što odlaže dijagnozu bolesti. Odgovor na lekove, vreme potrebno da se pacijent "negativizira" i prognoza isti su kod trudnica kao i kod žena koje nisu gravidne. *Perinatalna tuberkuloza.* Perinatalna tuberkuloza je ekstremno retka ako se sprovede efikasno lečenje u trudnoći, dok kod nelečenih trudnica perinatalna tuberkuloza može da ima fatalan ishod. Postavljanje dijagnoze perinatalne tuberkuloze često je problematično i teško. Jedan od razloga jeste i činjenica da su inicijalne manifestacije bolesti nespecifične a mogu se kasno javiti. U praksi, kongenitalna i perinatalna tuberkuloza imaju isti modus kliničkog ispoljavanja, leče se na isti način, sa istom prognozom. U postavljanju dijagnoze, epidemiološki podatak o aktivnoj tuberkulozi kod majke, ili nekog od članova domaćinstva, od neprocenjivog je značaja. Specifičnosti, odnosno razlike u imunoodgovoru fetusa i neonatusa, u odnosu na stariju decu, doprinose još težoj dijagnostici tuberkuloze u odnosu na odrasle. Tuberkulinski test kod dece neonatalnog uzrasta je negativan kod 75% inficirane dece**. Zaključak.** Ako se perinatalna tuberkuloza prepozna i leči prema postojećim protokolima, ishod je dobar.

Ključne reči: Tuberkuloza; Plućna tuberkuloza + kongenitalna; Trudnoća; Novorođenče; Odojče; Dijagnoza; Antituberkulotici; Infektivne komplikacije u trudnoći

Summary

Introduction. The number of people suffering from tuberculosis has increased rapidly in the whole world over the past three decades. The classical age distribution of disease has also changed. According to the epidemiological data the number of pregnant women having tuberculosis has also risen with the resulting increase in the incidence of perinatal tuberculosis. **Pregnancy and Tuberculosis.** The presentation of tuberculosis in pregnancy varies. The effects of tuberculosis on pregnancy depend upon various factors: site and extent of the disease, nutritional status and immune status of mother, concomitant diseases, stage of pregnancy when the treatment started and others. A delay between the onset and diagnosis occurs regularly. Treatment response, time to clearance of bacilli from sputum, and prognosis are similar to non pregnant women. **Prinatal tuberculosis**. Perinatal tuberculosis is extremely rare if the mother is effectively treated in pregnancy, but disease is usually fatal if untreated. Diagnosis of perinatal tuberculosis is very often problematic and difficult. The reason of this is the fact that the initial manifestations of disease are nonspecific and may be delayed. In practice, congenital and early neonatal infections have almost the same mode of presentations, treatment and prognosis. Epidemiological data on the active tuberculosis in mother or some other family member are of the utmost importance in diagnoing tuberculosis. Differences in immune responses in the fetus and neonate add to the diagnostic difficulties already recognised in young children. Tuberculin tests are negative in at least 75% of cases. **Conclusion.** If the condition is recognised and treated according to existing tuberculosis protocols, the outcome is favourable.

Key words: Tuberculosis; Tuberculosis, Pulmonary + congenital; Pregnancy; Infant, Newborn; Infant; Child; Diagnosis; Antitubercular Agents; Pregnancy Complications, Infectious

Uvod

Tuberkuloza (TB) je veoma značajan zdravstveni problem u svetu i kod nas. O tome govori podatak da se svake godine otkrije u svetu oko 8 miliona novih slučajeva, a od toga čak 3 miliona umire. Poslednjih decenija noviji epidemiološki podaci ukazuju na rastući trend tuberkuloze. Otkrićem efikasnijih lekova, javila se nada da će brzo doći do smanjenja broja obolelih, pa čak i do eradikacije. Nažalost to se nije desilo, već se javila paradoksalna situacija da danas ima više obolelih od ove bolesti nego prethodnih godina. Uzrok je rapidan rast svetske populacije, loši uslovi života, pandemija HIV-a, migracije i produžen životni vek u razvijenim zemljama. Najveći broj obolelih se beleži u zemljama Supsaharske Afrike, Jugoistočne Azije i Latinske Amerike [1,2]. Incidencija trudnica koje imaju ovu bolest je u porastu. Tuberku-

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Skraćenice

ATL	– antituberkulozni lekovi
ATT	– antituberkulozni tretman
DNK	– dezoksiribonukleinska kiselina
H	– izonijazid
MDR-TB	– multirezistentna forma tuberkuloze
R	– rifampicin
TB	– tuberkuloza
Mantoux	– tuberkulinski test

loza fetusa i novorođenčeta retka je ali kada dete oboli, bolest se može završiti smrtnim ishodom. Kao i u odrasloj populaciji, epidemiološka istraživanja su dokazala rastući trend TB među adolescentima i decom u Sjedinjenim Američkim Državama [3], a istraživanja u našoj zemlji dala su iste rezultate [4]. Prema istraživanju koje je sprovedeno u Vojvodini u periodu 1994–2003. godine, lečeno je 105 dece obolele od tuberkuloze; najveći broj obolelih je bio adolescentnog uzrasta 15–19 godina (39%) [4].

Mišljenja o uticaju bolesti na tok trudnoće menjala su se tokom vekova. Stav Hipokrata da trudnoća ima povoljan efekat na tok bolesti je bio opšteprihvaćen do 19. veka. Grisolle je saopštio sredinom 19. veka da je tok bolesti kod 24 trudnice bio lošiji u odnosu na grupu žena koje nisu bile trudne [5]. Početkom 20. veka mišljenja se menjaju. Smatralo se da trudnoća ima nepovoljan efekat na tuberkulozu, pa su se preporučivali prekidi trudnoće [6,7]. Započinjanjem hemioterapijske ere u lečenju tuberkuloze, Hedval je objavio da je kod 250 trudnica obolelih od tuberkuloze nađeno poboljšanje kod 9%, pogoršanje kod 7% i neizmenjen tok kod 84% pre porođaja, a 9% poboljšanja, 15% pogoršanja i 76% nepromenjenog toka bolesti posle porođaja [8]. Studija urađena u Londonu, 1950. godine (Pridie, Stradling) pokazala je da je procenat tuberkuloze isti kod trudnica kao i kod žena koje nisu bile gravidne. Podaci koje je objavio San Domingo (1996) ukazuju na to da su postpartalno žene pozitivne na HIV i žene negativne na HIV pod istim rizikom od obolevanja od tuberkuloze [9]. Savremene studije podržavaju stav da tuberkuloza, posebno ekstrapulmonalna tuberkuloza trudnice nosi rizik od povećanja broja antenatalnih hospitalizacija, prevremenog porođaja, maternalnog mortaliteta, perinatalnog mortaliteta dece u odojčadskom uzrastu i intrauterinog zastoja u rastu u odnosu na decu žena koje nisu imale tuberkulozu [10–12].

Ovaj članak daje osvrt na ključne aspekte perinatalno stečene tuberkuloze, odnosno mogućnosti ranog otkrivanja bolesti, kliničku sliku tuberkuloze u neonatalnom periodu, tretman i ishod bolesti.

Tuberkuloza i trudnoća

Tokom lečenja tuberkuloze trebalo bi izbegavati začeće, ali se ne treba plašiti ukoliko do trudnoće dođe. Aktivna tuberkuloza nije indikacija za terapijski abortus, pošto se ova bolest uspešno leči. Nelečena tuberkoloza predstavlja veliki rizik i za trudnicu i za fetus. Klinička slika tuberkuloze u trudnoći varira: neke žene nemaju simptome bolesti, veći broj žena ima nespecifične simptome u vidu slabosti i letargije, a kod nekih trudnica su simptomi teži, tipični za tuberkulozu. Bolest se najčešće ispoljava kao plućna forma, ali je ekstrapulmonalna tuberkuloza kod trudnica češća (10–15%) u odnosu na populaciju koja nije gravidna [12]. Primećeno je da se kod trudnica češće ispoljava negativan rezultat tuberkulinskog testa, verovatno kao posledica izmenjenog imunoodgovora na *Mycobacterium tuberculosis* [13]. Skoro po pravilu djagnoza se postavlja kasnije u odnosu na vreme pojave prvih simptoma bolesti trudnice. Ova činjenica je rezultat nespecifičnih simptoma, izostanka ili izbegavanja radiografskih pretraga u trudnoći ili niskog indeksa sumnje na postojanje tuberkuloze. Odgovor na antituberkuloznu terapiju i vreme koje je potrebno da se postigne obeskličavanje (negativizacija) sputuma isto je kod trudnica kao i kod žena koje nisu gravidne, kao i prognoza u slučajevima ranog započinjanja lečenja.

U slučaju ekspozicije bacilima tuberkuloze (kontakt I reda) trudnica sa pozitivnim tuberkulinskim (*Mantoux*) testom, klinički bez simptoma bolesti i sa urednim radiološkim nalazom, treba da primi hemioprofilaksu u skladu sa nacionalnim vodičima za lečenje ove bolesti.

Ako se dokaže aktivna tuberkuloza, treba započeti antituberkulozni tretman (ATT). Neki autori savetuju odlaganje započinjanja lečenja u ranoj trudnoći, do drugog trimestra i to ukoliko je žena dobro. Međutim većina se slaže da je korist od lečenja tuberkuloze, preveniranje maternalnog morbiditeta i mortaliteta i sprečavanje perinatalne transmisije infekcije, značajnija od mogućeg teratogenog efekta. Brojne strudije su dokumentovale da teratogeni efekat ATT *in utero* i procenat dece rođene sa kongenitalnim malformacijama usled dejstva antituberkulozne terapije, nije zabrinjavajući [14–16].

Žena koji doji, a ima tuberkulozu, treba da dobija pun ATT. Svi antituberkulinski lekovi (ATL) prelaze u mleko i ne ugrožavaju dojenje. Njihove koncentracije u mleku su niske, efekat na novorođenčeta mali, a potencijalno toksični efekti na dete koje sisa nisu objavljeni. Da bi se snizio nivo ATL kod novorođenčeta, majka može uzeti lek odmah nakon podoja i dati flašicu za sledeći obrok, a onda se vratiti na uobičajeni ritam hranjenja do sledećeg dana [17].

Perinatalna tuberkuloza

Definicija i ispoljavanje perinatalne/kongenitalne tuberkuloze kod dece do 12 meseci

Definicija kongenitalne tuberkuloze je uvek bila predmet kontroverzi. Kriterijumi koji su još uvek važeći za definisanje ovog kliničkog entiteta su sledeći: novorđenče mora imati potvrđenu tuberkulozu i bar još jedan nalaz od sledećih: 1) primarni kompleks u jetri ili kazeozni granulom u jetri, 2) tuberkuloznu infekciju placente ili maternalnog genitalnog trakta, 4) isključenu mogućnost postnatalnog prenošenja bolesti bliskim aktivnim tuberkuloznim kontaktom, 5) dokazane patološke promene u prvoj nedelji života [26]. Prenošenje infekcije se dešava ili *in utero* hematogenim širenjem preko umbilikalne vene ili ingestijom infici-

rane amnionske tečnosti; tokom porođaja aspiracijom ili ingestijom inficirane amnionske tečnosti, direktnim kontaktom sa inficiranim tkivom cerviksa i/ili endometrijuma, ili postpartalno inhalacijom bacila, ili ingestijom inficiranog sadržaja iz inficiranog izvora. Zbog ovih poteškoća u određivanju tačnog vremena i okolnosti javljanja infekcije kod deteta, u novije vreme, perinatalna tuberkuloza se uglavnom definiše kao TB stečena *in utero, intrapartum* ili tokom ranog neonatalnog perioda. Drugim rečima, termin perinatalna tuberkuloza je zamenjen terminom kongenitalna tuberkuloza. Tačno vreme nastanka infekcije nije od krucijalnog značaja, pošto su klinička slika, dijagnostika, terapija i prognoza slični.

U skladu sa podacima iz literature, simptomi se generalno počinju ispoljavati u drugoj ili trećoj nedelji života i to pojavom febrilnosti, gubitkom na telesnoj masi, razdražljivošću, znacima respiratornog distresa, gubitkom apetita, bledilom, bleđim stolicama, tamnijom mokraćom i žuticom. Takva deca imaju opstruktivnu žuticu zbog primarnog fokusa u jetri i opstrukcije žučnih puteva uvećanim limfnim čvorovima. Često deca imaju u uzrastu 2−4 nedelje nejasno febrilno stanje, znake respiratornog distresa i hepatosplenomegaliju zbog čega se leče brojnim antibioticima zbog sumnje na sepsu. Ako je dete inficirano odmah nakon rođenja, posle asimptomatskog perioda koji može da traje 3-4 nedelje, javlja se klinička slika akutne pneumonije sa kašljem, cijanozom i brzom progresijom simptoma. Ukoliko ne postoji podatak da majka ima bolest, lečenje može da bude problematično sa lošim odgovorom na nespecifične lekove [17,21].

Prevencija

Perinatalna tuberkuloza je ekstremno retka kod dece majki koje su lečene i kod kojih je dijagnoza postavljena na vreme. Prema stavovima Svetske zdravstvene organizacije, majka nije više infektivna nakon lečenja od 2-3 nedelje [18]. Ako se dijagnoza postavi neposredno nakon rođenja deteta, dete i placenta se detaljno moraju pregledati radi utvrđivanja znakova perinatalne tuberkulozne infekcije, a ako ima bilo kakvih sumnji ili dilema, dete se leči empirijski. Sva ova deca se moraju pratiti klinički, tokom dve godine [19].

Postupci kod dece ispod 12 meseci, koje je rodila majka sputum-pozitivna na bacilus Koch

Klinički postojanje bolesti se dokazuje na osnovu: postojanja kliničkih simptoma bolesti, rezultata tuberkulinskog testa, radiološkog nalaza, direktnih mikroskopskih pregleda preparata bojenih metodom *Ziehel-Nelsen*, mikrobioloških nalaza gastričnih lavata – najmanje 4 uzorka. Ukoliko je potrebno, treba uraditi lumbalnu punkciju, uzeti uzorak placente na mikrobiološki i patohistološki pregled i dr.

Ako se bolest dokaže, lečiti dete isto kao i u slučaju postojanja perinatalne-kongenitalne tuberkuloze (dati punu ATT).

Ako se kod deteta ne dokaže bolest, ono se svrstava u visokorizičnu novorođenčad za obolevanje od diseminovane TB koju treba lečiti. U literaturi se preporučuju različiti profilaktički terapijski režimi. Prilikom donošenja odluke kako lečiti dete važno je da se proceni mogući rizik od razvoja bolesti. Britansko torakalno udruženje (BTS) u svom vodiču za lečenje tuberkuloze preporučuje upotrebu izomijazida (H) u dozi od 5 mg/kgTM, 3 meseca [20]. Takođe je moguće novorođenčetu koje izgleda zdravo, uključiti H 5 mg/kgTM u jednoj dnevnoj dozi, tokom 2 meseca. Potom se radi tuberkulinski test. Ako je on negativan, lek se isključuje

Tabela 1. Efekat ATT u trudnoći, laktaciji i kod novorođenčeta
Table 1. *Anti-tuberculous drugs in pregnancy, lactation and in newborn*

Lek/*Drugs*	Trudnoća/*Pregnancy*	Laktacija/*Lactation*	Novorođenče/*Newborn*
Rifampicin (R) *Rifampicin*	Siguran *Safe*	0,5% adultne doze detektovano/*0.5% of adult dose detected*	Siguran u dozi 10–20 mg/kg/dan *Safe in dosis 10 – 20 mg/kg/day*
Izonijazid (H) *Isoniazid*	Siguran *Safe*	0,75-2,3% adultne doze detektovano/*0.75-2.3% of adult dose detected*	Siguran u dozi od 5−10 mg/kg/dan *Safe in dosis 5-10 mg/kg/day*
Pirazinamid (Z) *Pyrazinamide*	Podaci ograničeni, preporučuje se *Limited-data, recomended*	0,75-2,3% adultne doze detektovano/*0.75-2.3% of adult dose detected*	Siguran u dozi od 20−30 mg/kg/dan *Safe in dosis 20-30 mg/kg/day*
Etambutol (E) *Ethambutol*	Siguran *Safe*	Vrlo niske koncent *Very-low concentrations*	Ne preporučuje se (retrobulbarni neuritis)/*Not recomanded (retrobulbar neuritis)*
Amikacin *Amicacin*	Ototoksičan? *Ototoxicity?*	Da, koncentracije nepoznate *Yes,concentations unknown*	Delimična resorpcija u digestivni trakt *Partial resorption in digestiv tract*
Streptomicin (S) *Strepotomycin*	Ototoksičan? *Ototoxicity?*	0,95-22,5% *0.95-22.5%*	Siguran? *Safe?*
Hinoloni *Hinoloni*	Abnormalnosti kostiju (životinje)/*Bone abnormalities (animals)*	0,05-0,5% adultne doze *0.05-0.5% of adult dose*	Sigurnost TH 5−10 dana; oprezno! *Safe TH from 5-10 days; beware!*

i daje se BCG vakcina. Ako je tuberkulinski test pozitivan, lečenje se nastavlja još 4 meseca. Vakcinisanje BCG vakcinom ne treba sprovoditi dok traje lečenje izonijazidom. Ukoliko se dete ne podvrgne tuberkulinskom testiranju, lečenje primenom H se produžava na 6 meseci [21]. Navodi se i mogućnost lečenja ove kategorije novorođene dece i odojčadi (mlađe od 2 meseca) sa 2 leka, H+rifampicin (R), u toku 3 meseca. Posle tromesečne terapije treba uraditi tuberkulinski test, i ako je on negativan dete treba vakcinisati. Terapija primenom H ne utiče na imunogenost BCG vakcine [22].

Profilaksa izonijazidom je efikasna pa stoga nije potrebno odvajanje deteta od majke, nakon započinjanja davanja leka. Dojenje se ne prekida. Ako majka uzima H i R, iako se izlučuju putem mleka, njihove koncentracije su tako male da ne utiču na dete (nemaju profilaktički efekat, ne menjaju koncentracije lekova koje dete uzima, ne ispoljavaju toksične efekte).

Deca čije su majke primile kompletnu terapiju za tuberkulozu tokom trudnoće i smatraju se zdravim, i deca majki sa Mantoux+, bez znakova bolesti

Izuzetno je važno da se provere svi članovi domaćinstva na prisustvo moguće infekcije. Ako se skrining domaćinstva sprovede i bolest isključi, dete ne zahteva uvođenje profilakse i može da se vakciniše.

Ukoliko se skrining na tuberkulozu iz nekih razloga ne sprovede, indikovana je profilaksa deteta (preporuka za režim H R) koja se sprovodi sve do isključenja aktivne bolesti. Odojče može biti testirano posle 6 nedelja i, ako je negativno, može se dati BCG vakcina. Profilaksa se može sprovoditi sve dok u domaćinstvu ima potencijalno kontagioznih odraslih osoba koje su u kontaktu sa detetom.

Deca bez simptoma, majke sa Mantoux+, sputum negativne na bacilus Koch sa urednim rentgenskim snimkom pluća

Dete ostaje uz majku. Ne prima lekove. Prima BCG vakcinu. Treba ispitati sve članove domaćinstva na prisutvo aktivne bolesti. Ako se bolest kod članova porodice dokaže, potrebno je vršiti kontrolna tuberkulinska testiranja.

Deca bez simptoma, majke sa Mantoux+ i pozitivnim rentgenskim nalazom

Odvojiti dete od majke, dok se ne utvrdi ili otkoloni postojanje bolesti.

Ako majka ima tuberkulozu, dete se svrstava u visokorizičnu kategoriju pa je postupak, po protokolu za praćenje visokorizične dece ili lečenje perinatalne tuberkuloze, ako postoji dokaz za postojanje bolesti deteta.

Ako majka nema bolest, dete ne zahteva terapiju, ali je potrebno praćenje deteta zbog mogućeg rizika. Praćenje se vrši tuberkulinskim testiranjima na svaka tri meseca u prvoj godini, potom jednom godišnje. Treba pratiti i eventualne kliničke promene kod deteta. Potrebno je uraditi i skrining članova familije na prisustvo aktivne bolesti.

Procenu o potrebi lečenja majke, u ovom slučaju, obavlja pulmolog [3,23,24].

Kontrola infekcije u porodilištu

U kontekstu kasnog postavljanja dijagnoze perinatalne tuberkuloze, brojni autori su diskutovali o riziku za obolevanje zdravih novorođenčadi u porodilištu i jedinicama intenzivne nege u bolnicama. Uprkos niskom stepenu transmisije u jedinicama intenzivne nege i porodilištima, savetuje se upotreba izolacionih boksova i provetravanje prostora [17,23].

Laartz i saradnici su objavili rad koji predstavlja sažetak literature koja se odnosi na ovaj problem i doneli su zaključak da je potrebno aktivno i ažurno praćenje sve novorođne dece pod rizikom, tuberkulinsko testiranje na 3 meseca i profilaksa uvođenjem H čak i kod dece kod kojih je tuberkulinski test negativan [25]. Profilaksa se kod ove dece sprovodi 3 meseca, test se ponavlja, pa ako je rezultat negativan profilaksa se prekida. Ukoliko je kožni test veći od 5 mm, treba započeti ispitivanja za dokazivanje bolesti. Ako se jave simptomi bolesti, treba započeti lečenje. Ako simptoma bolesti nema a test je pozitivan, treba započeti sa hemoprofilaksom u trajanju od 6 meseci.

Dijagnostika perinatalne TB

Postavljanje dijagnoze perinatalne TB nije lako, posebno kod dece sa negativnim tuberkulinskim testom i nespecifičnom kliničkom slikom. Kod odojčadi dijagnostika se zasniva na rezultatu tuberkulinskog testa, koji je često negativan (i do 78%), za razliku od starije dece i adolescenata. Prema rezultatima istraživanja koje je sprovedeno kod dece i adolescenata obolelih od plućne TB u Vojvodini, u periodu 1994−2003. godine, tuberkulinski test bio je pozitivan kod 79% slučajeva [4]. U slučaju sumnje na perinatalnu tuberkulozu, kod novorođene dece i mlade odojčadi sa negativnim testom, test treba ponoviti za 3 meseca. Kod većine dece dobija se konverzija nalaza − test postaje pozitivan. Radiološke pretrage su indikovane ukoliko postoje izraženi simptomi bolesti. Kod perinatalne tuberkuloze rendgenski snimak pluća je skoro uvek patološki, sa prisutnim milijarnim rasapom u oko 50% slučajeva [27]. Uzorci gastričnih lavata, bronholavata, tečnosti iz abdomena u slučaju postojanja ascitesa, bioptički materijal uvećanog limfnog čvora, likvor i dr., pregledaju se direktno mikroskopski na prisustvo acido-rezistentnih bacila i kultivišu se na odgovarajućoj podlozi za izolaciju *Mycobacterium tuberculosis*. Vrednost gastričnih lavata kod neonatusa, kao uzorka za dokazivanje tuberkuloze, znatno je veća nego kod starije dece (70% pozitivnih nalaza), i dobro se toleriše kao procedura [28−30]. U slučajevima kada je dijagnoza nejasna, postoje radiološke promene i sumnja se na tuberkulozu, treba uraditi i bronhoskopiju kojom stičemo uvid u stanje disajnih puteva i uzimamo ispirak iz disajnih puta za citološki i bakteriološki pregled [31]. Kontroverzna su mišljenja o tome da li su uzorci gastrolavata vredniji kao materijal za mikrobiološka ispitivanja, u od-

nosu na bronholavat, kod dece. Prema istraživanju rađenom u Vojvodini 2006. godine, kod dece uzrasta od 6 meseci do 18 godina, hospitalizovane zbog sumnje na tuberkulozu, mikrobiološke kulture bronholavata su bile pozitivne u većem broju slučajeva nego kulture gastrolavata (73% vs 55%) [32].

Pošto ova klasična bakteriološka dijagnostika traje dugo, nekada i duže od 2 meseca, ukazala se potreba za uvođenjem novih, brzih metoda. Razvijeni su novi sistemi za izolaciju mikobakterija koji koriste tečne hranljive podloge (*BACTEC i MGIT-Becton Dickinson, BacT/Alert, Biomerieux*, i dr). Ovi testovi skraćuju vreme identifikacije bacila na 2 nedelje. Šira primena ovih metoda je ograničena visokom cenom aparature. U odabranim slučajevima u dijagnostici se može koristiti molekularna tehnika − reakcija lančane polimerizacije dezoksiribonukleinske kiseline (DNK) − *polymerase chain reaction* (PCR) koja se zasniva na umnožavanju određenog genoma bacila tuberkuloze i njegovoj detekciji na gelu. Troškovi za izvođenje ove metode su još uvek veliki, te je primena opravdana samo u velikim mikrobiološkim laboratorijama. Iz kultura se bacil tuberkuloze može identifikovati na osnovu detekcije specifičnih sekvenci nukleinskih kiselina bacila (za nekoliko sati). U te svrhe koriste se komercijalno dostupne DNK probe za *Mycobacterium tuberculosis* koje se zasnivaju na sposobnosti vezivanja gen-probe (segment DNK mikobakterije) za komplementarni segment ribonukleinske kiseline mikobakterija. U dijagnostici je u upotrebi i standardizovana metoda genotipizacije *Mycobacterium tuberculosis* izolata kojom se vrši analiza polimorfizma insercione sekvence IS6110 u genomu ove bakterije (tehnika polimorfizma dužine restrikcionih fragmenata − RFLP). Ove dve poslednje, molekularne tehnike treba primeniti kao nadogradnju konvencionalnih tehnika ali one ne mogu u potpunosti da zamene kultivisanje uzoraka [33,34].

Lečenje perinatalne tuberkuloze

Perinatalna tuberkuloza se završava smrtnim ishodom ukoliko se ne prepozna i ne leči. Nakon sprovođenja dijagnostike, započinje se empirijsko lečenje deteta u skladu sa nacionalnim preporukama. Pošto se ne radi o čestoj patologiji, ne postoje izgrađeni jasni terapijski stavovi o lečenju perinatalne tuberkuloze koji bi definisali optimalne doze lekova i dužinu trajanja terapije. Opisani su slučajevi potpunog oporavka deteta nakon primene standardnog režima od 2 meseca lečenja primenom 4 leka (HRZS − izonijazid, rifampicin, pirazinamid, streptomicin) i 4 meseca primenom 2 leka (HR) [19]. Daju se i predlozi da se nastavak lečenja primenom HR nastavi ukupno 6 meseci [17]. Ovo se odnosi na forme ekstrapulmonalne tuberkuloze. Dužina lečenja određuje se na osnovu kliničke slike i odgovora na lekove. Praćenje deteta u bolnici podrazumeva kontrole biohemijskih nalaza i rentgenskih nalaza pluća na svakih mesec dana, a ukupno praćenje deteta sa ovom formom tuberkuloze treba da traje do 2 godine [35,36].

Pošto je, kako je već navedeno, kod novorođenčeta teško iskultivisati bacil, u započinjanju terapije rukovodimo se rezultatima mikrobioloških nalaza dobijenih kod majke. Za razliku od dece starijeg uzrasta koja imaju adekvatne koncentracije vitamina B u organizmu, novorođenoj deci na prirodnoj ishrani koja primaju izonijazid, treba dodati piridoksin koga nema dovoljno u majčinom mleku.

Poseban izazov su slučajevi pacijenata obolelih od multirezistentnih formi tuberkuloze (MDR-TB), kod kojih su bacili tuberkuloze rezistentni na izonijazid i rifampicin, kao i pacijenti sa ekstenzivnom rezistencijom na antituberkulozne lekove kod kojih su sojevi bacila tuberkuloze rezistentni takođe i na fluorohinolone i na bar još jedan lek iz rezervne grupe lekova koji se koriste u lečenju bolesti (amikacin, kanamicin).

Kod novorođenčeta sa MDR-TB trajanje terapije se produžava, 12−18 meseci [23,24].

Ukoliko je stanje deteta teško i zahteva intenzivnu negu i nadzor, potrebno mu je u suportivnoj terapiji dati kiseonik ili respiratornu ventilacionu potporu. Kortikosteroidi se dodaju deci sa tuberkuloznim meningitisom i tuberkulozom limfnih čvorova koja uzrokuje simptome opstrukcije disajnog puta.

Zaključak

Perinatalna tuberkuloza je izuzetno ozbiljna i potencijalno fatalna bolest. Ukoliko postoji visok indeks sumnje na postojanje bolesti kod dece čije majke boluju od tuberkuloze, ili kod kojih postoji sumnja na ovu bolest i, ako se započne agresivna terapija prema protokolu, prognoza perinatalane tuberkuloze je dobra. Briga o novorođenčetu sa perinatalnom tuberkulozom počinje skriningom i lečenjem trudnica sa plućnom tuberkulozom. Neonatolozi i pedijatri treba da imaju na umu da treba voditi računa o kontroli infekcije u porodilištima, bez obzira što je mogućnost transmisije u ovim okolnostima niska, kao i da veću pažnju usmere na mogućnost postojanja bolesti kod trudnica iz loših socioekonomskih kategorija i neposredno doseljenih iz endemskih zemalja (Bosna i Hercegovina, Rumunija, Ukrajina, i dr.)

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DIJABETESNA KETOACIDOZA KOD DECE S NOVOOTKRIVENIM DIJABETESOM TIP 1 U CRNOJ GORI 1999–2008. GODINE

DIABETIC KETOACIDOSIS IN CHILDREN WITH NEWLY DETECTED TYPE 1 DIABETES IN MONTENEGRO FROM 1999 TO 2008

Mira SAMARDŽIĆ[1], Nataša TERZIĆ[2] i Milena POPOVIĆ[1]

Sažetak

Uvod. Cilj rada je analiza prevalencije dijabetesne ketoacidoze u periodu od 10 godina (1999–2008. godine) kod dece sa novootkrivenim dijabetesom u Crnoj Gori. **Materijal i metode.** Sprovedena je retrospektivna populaciona studija. Podaci o pacijentima su uzeti iz dva nezavisna izvora: otpusna pisma i registar dece obolele od dijabetesa. Laboratorijski nalazi su rađeni pre prve injekcije insulina: glukoza u krvi, gasne analize krvi, elektroliti, kreatinin, insulin, C-peptid i glikozilirani hemoglobin. Dijabetesna ketoacidoza je definisana kao pH <7,3, a teška kao Ph <7,1. U statističkoj obradi podataka korišćen je *statistički program SPSS for Windows* (verzija 17). **Rezultati.** Tokom ispitivanog perioda registrovano je 208 dece mlađe od 15 godina (107 dečaka i 101 devojčica) sa novotkrivenim dijabetesom tip 1. Stopa incidencije prema uzrastu i polu bila je 15,8/100 000/god. Od njih je 51 (24,5%) imalo dijabetesnu ketoacidozu u vreme postavljanja dijagnoze, a 8 dece (3,8%) imalo je tešku formu. Smrtnih slučajeva nije bilo. Kod dece mlađe od 5 godina prevalencija dijabetesne ketoacidoze bila je 30,4%. Nije nađena statistički značajna korelacija između učestalosti dijabetesne ketoacidoze, vrednosti pH i starosti dece (p>0,05). Takođe nije nađena značajna razlika u učestalosti dijabetesne ketoacidoze između dečaka i devojčica (p>0,05). **Zaključak.** Učestalost dijabetesne ketoacidoze kod dece sa novootkrivenim dijabetesom u Crnoj Gori još uvek je velika, sa tendencijom smanjenja poslednjih 10 godina. Posebno su pod rizikom deca mlađa od 5 godina.

Ključne reči: Dijabetesna ketoacidoza; Dijabetes melitus tip 1; Dete; Crna Gora; Prevalenca; Muško; Žensko; Šećer u krvi; Gasne analize krvi

Summary

Introduction. The aim of the study was to analyze the prevalence of diabetic ketoacidosis during the period of 10 years (1999-2008) among children diagnosed with type 1 diabetes in Montenegro. **Material and Methods.** A retrospective population–based incidence study was performed. The study participants were selected from two independent sources: the diabetes register and hospital records. The following parameters were measured before the first insulin injection: plasma glucose, blood gas analysis, electrolytes, creatinine, insulin, c-peptide, and HbA1c. Diabetic ketoacidosis was defined as pH <7.3 and severe diabetic ketoacidosis as pH <7.1. The obtained data were analysed using SPSS for Windows (version 17). **Results.** During the study period, 208 children <15 years of age (107 boys and 101 girls) were found to have newly diagnosed type 1 diabetes. The age- and sex-standardized incidence rate was 15.8/100,000 children/yr. Of these, 51 (24.5%) presented with diabetic ketoacidosis at the time of diagnosis and 8 (3.8%) had a severe form, and no one died. In children <5 years the prevalence was 30.4%. We found no statistically important correlation between diabetic ketoacidosis incidence, pH value and the age of children (p>0.05). There was also no significant difference in diabetic ketoacidosis incidence between the boys and girls (p>0.05). **Conclusion.** The frequency of diabetic ketoacidosis in children with newly diagnosed type 1 diabetes in Montenegro is still high with a trend to decrease in the last ten years. In particular, children under 5 years of age are at a high risk of developing diabetic ketoacidosis at the onset.

Key words: Diabetic Ketoacidosis; Diabetes Mellitus, Type 1; Child; Montenegro; Prevalence; Male; Female; Blood Glucose; Blood Gas Analysis

Uvod

Dijabetes melitus je grupa metaboličkih bolesti čija je glavna osobina hronična hiperglikemija koja nastaje kao posledica poremećene sekrecije insulina, delovanja insulina ili oboje [1]. Dijabetes melitus tip 1 (DMT1) najčešće se javlja kod dece i mladih. To je autoimuno oboljenje koje dovodi do destrukcije insulin-sekretujućih β-ćelija pankreasa i kompletnog ili gotovo kompletnog deficita in-

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Skraćenice

DKA	− dijabetesna ketoacidoza
DMT1	− dijabetes melitus tip 1
HbA1c	− glikozilirani hemoglobin
IKR	− interkvartilni rang

sulina. Incidencija dijabetesa tipa 1 u Crnoj Gori poslednih 5 godina je među najvećim na Mediteranu (17,5/100 000) i progresivno raste za oko 6,5% (95% IP : 1,6−11,7) godišnje [2] .

Dijabetesna ketoacidoza (DKA) glavni je uzrok mortaliteta i morbiditeta kod dece sa DMT1. Nastaje kao posledica apsolutnog ili relativnog nedostatka insulina u kombinaciji sa efektima povišenog nivoa kontraregulatornih hormona: kateholamina, glukagona, kortizola i hormona rasta [3]. Postoje velike geografske varijacije u učestalosti DKA kod dece sa novootkrivenim dijabetesom u Evropi i Severnoj Americi: 15−67%. Češće se javlja kod dece mlađe od 5 godina i kod dece nižeg socioekonomskog statusa [4].

Cilj ovog istraživanja bio je da se ustanovi učestalost DKA i klinička prezentacija dijabetesa tipa 1 kod dece u Crnoj Gori u vreme postavljanja dijagnoze tokom perioda od 10 godina (1999−2008.).

Materijal i metode

Od 1990. godine sva deca sa novootkrivenim dijabetesom iz Crne Gore se hospitalizuju na Institutu za bolesti dece u Podgorici. Podaci o pacijentima su uzeti iz dva nezavisna izvora: registar za dijabetes tip 1 i otpusna pisma iz bolnice. Klinički i laboratorijski nalazi su analizirani retrospektivno kod dece mlađe od 15 godina koji su prilikom postavljanja dijagnoze dijabetesa i prve hospitalizacije imali dijabetesnu ketoacidozu. Kod svih je pacijenata nakon uzimanja laboratorijskih nalaza odmah započeta insulinska terapija. Laboratorijski nalazi su rađeni standardnim laboratorijskim metodama u kliničkoj laboratoriji Instituta za bolesti dece u Podgorici. Pre prve injekcije insulina određivani su: glukoza u krvi, gasne analize, elektroliti, kreatinin u serumu, insulin, C-peptid i glikozilirani hemoglobin (HbA1c). Glukoza u krvi je određivana enzimskom metodom (sa heksokinazom), gasne analize iz arterijske krvi su analizirane potenciometrijom, elektroliti su određivani metodom jon-selektivne eletrode a kreatinin enzimskom kolorimetrijskom metodom. Insulin i C-peptid su određivani metodom hemiluminiscencije (CLIA) a HbA1c imunoturbidimetrijski iz hemolizata pune krvi.

Studiju su odobrili lokalni Etički komitet i Uređivački odbor matične institucije.

Biohemijski kriterijumi za postavljanje dijagnoze DKA su: hiperglikemija (> 11 mmol/l), pH < 7,3 ili bikarbonati plazme < 15 mmol/l, ketonemija i ketonurija. Prema težini DKA se deli na blagu (pH < 7,3, bikarbonati < 15 mmol/l), srednje tešku (pH < 7,2, bikarbonati < 10 mmol/l) i tešku (pH < 7,1, bikarbonati < 5 mmol/l) [3].

Dobijeni podaci su analizirani primenom statističkog softverskog paketa SPSS (*for Windows version 17*). Za testiranje značajnosti razlike, povezanosti i poređenje različitih starosnih grupa (0−4 godine, 5−9 i 10−14 godina) u odnosu na prisustvo DKA korišćeni su t -test za nezavisne uzorke, χ^2-test, linearne Pirsonove korelacije i jednofaktorska analiza varijanse.

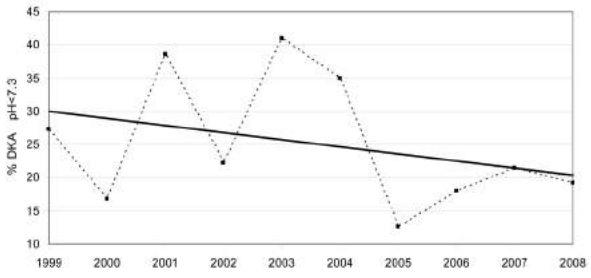
Rezultati

Tokom perioda praćenja u Crnoj Gori je dijagnostikovano 208 dece sa dijabetesom melitus tip 1 i to 107 (51,4%) dečaka i 101 (48,6%) devojčica (p > 0,05). Prosečna starost bila je 7,8±3,9 godina. Četrdeset šestoro dece (22,1%) bilo je mlađe od 5 godina, 75 (36%) imalo je između 5 i 9 godina, a 87 (41,8%) imalo je 10−14 godina. Ako se kao kriterijum za dijabetesnu ketoacidozu uzme pH < 7,3, u vreme postavljanja dijagnoze DKA je imalo 51 dete (24,5%) a teška DKA nađena je kod 8 dece (3,8%). Nije nađena statistički značajna razlika u učestalosti DKA između dečaka (28,7%) i devojčica (20,6%) (p > 0,05). Takođe ne postoji značajna razlika u uzrastu u kome se javljala DKA na početku bolesti kod dece različitog pola (p > 0,05).

Kada se uporede različite starosne grupe (0−4, 5−9 i 10−14 godina) učestalost DKA (30,4%) i teškog oblika DKA (6,5%) veća je kod dece najmlađe starosne grupe, ali razlika nije statistički značajna (p > 0,05).

Srednja vrednosti pH u krvi kod sve dece sa DKA bila je 7,2 (95% CI : 7,1−7,2), u starosnoj grupi 0−4 god. 7,1 (95% CI : 7−7,2), 5−9 god. 7,2 (95% CI : 7,1−7,3) i 10−14 god. 7,2 (95% CI : 7,1−7,2). Nije nađena statistički značajna korelacija između starosti dece i vrednosti pH (p > 0,05).

Prisustna je tendencija smanjenja učestalosti obolevanja u ispitivanom periodu (**Grafikon 1**).



Grafikon 1. *Prevalencija DKA kod dece sa novootkrivenim DMT1 u Crnoj Gori 1999−2008. godine*

Graph 1. *Annual proportion of children with DKA having type 1 diabetes in Montenegro in 1999-2008.*

Laboratorijski nalazi kod dece sa novootkrivenim dijabetesom tipa 1 prikazani su u **Tabeli 1**.

Tabela 1. Učestalost *dijabetesne ketoacidoze i laboratorijski nalazi u vreme postavljanja dijagnoze kod različitih starosnih grupa*
Table 1. *Frequency of diabetic ketoacidosis and laboratory data at the time of making diagnosis by age group*

Laboratorijski nalazi *Laboratory findings*	0−4 god.	5−9 god.	10−14 god.	0−14 god.	p
Broj pacijenata sa DKA *No of patients with DKA*	14/46	16/75	21/87	51/208	<0,05
DKA (%) Ph<7.3	30,4	21,3	24,1	24,5	<0,05
DKA (%) Ph < 7.1	6,5	2,7	3,4	3,8	<0,05
Ph krvi/*Blood Ph* (95%IP)*	7,1 (7−7,2)	7,2 (7,1−7,3)	7,2 (7,1−7,3)	7,2 (7,1−7,3)	<0,05
Glukoza u krvi † *Blood glucose* [mmol/l (IKR)]	21,4 (19,3−31,2)	22,6 (17,6−27,2)	18,7 (16,4−24,8)	21,4 (17,6−26,6)	>0,05
Bikarbonati † *Bicarbonates* [mmol/l (IKR)]	7,2 (4,5−10)	9,5 (4,4−12,6)	8,5 (6,2-10,5)	7,9 (5,3−10,5)	>0,05
HbA1c* [% (95%IP)]	10,9 (8,9−12,9)	11,1 (9,5−12,7)	13,5 (11,9−15,2)	12 (11−13)	<0,05
c-peptid † [mmol/l (IKR)]	0,16 (0,1−0,2)	0,15 (0,1−0,3)	0,21 (0,1−0,3)	0,18 (0,1−0,25)	>0,05

Podaci su prikazani kao procenat, srednja vrednost i 95% interval poverenja (IP)*, ili medijana i interkvartilni rang (IKR) †
Data are given in percents, mean values and 95% of confidence interval or median and interquartile range †

Diskusija

Crna Gora spada u Evropske zemlje sa srednjim rizikom za nastanak dijabetesa tipa 1 [5]. Standardizovana incidencija je 1999−2003. godine bila 14/100 000, a 2004−2008. godine 17,5/100 000, sa godišnjim rastom od 6,5% [6]. Prevalencija DKA (pH < 7,30) u našoj studiji bila je 24,5%, a tešku DKA imalo je 3,8% dece. DKA se najčešće (30,4%) javlja kod dece mlađe od 5 godina a ređe kod dece uzrasta 5−9 godina (21,3%), ali te razlike nisu statistički značajne (p > 0,05). U većini studija je saopšteno da su deca mlađa od dve godine pod većim rizikom za DKA na početku bolesti a taj rizik je prisutan do pete godine života [7]. Zbog relativno malog broja ispitanika, mi nismo posebno posmatrali starosnu grupu mlađu od dve godine. Razlozi što se DKA češće javlja u mlađoj starosnoj grupi su višestruki. U tom uzrastu lekari ređe posumnjaju na dijabetes a dekompenzacija kao posledica dehidratacije i acidoze se razvija brže. Pored toga, destrukcija β-ćelija u toj populaciji je agresivnija a vrednosti C-peptida su niže nego kod starije dece, što je slučaj i kod naših ispitanika. U izveštajima *Epidemiology and Prevention of Diabetes study* (EURODIAB) projekta koji obuhvata 24 evropske zemlje, učestalost DKA (Ph < 7,3) u 11 centara bila je 40% sa varijacijama 26−67% [8]. U Finskoj, koja ima najveću incidenciju dijabetesa tipa 1 u svetu prevalencija DKA (pH < 7,3) bila je 2002−2005. godine 19,4% a teške DKA − 4,3%. Paradoksalno je da u Finskoj u tom periodu zabeležena je i najmanja učestalost DKA kod dece mlađe od 5 godina (16,5%) [9, 10]. Dijabetesna ketoacidoza (1995−2007. g.) još uvek je česta kod dece sa novootkrivenim dijabetesom u Austriji i Nemačkoj − 21,1%, a 5,9% dece u tim zemljama imalo je tešku DKA [11,12]. Prema dostupnim podacima u odnosu na neke zemlje bivše Jugoslavije, u Crnoj Gori se ređe javlja dijabetesna ketoacidoza u vreme postavljanja dijagnoze DMT1. U Bosni i Hercegovini (kanton Tuzla) od 1990. do 2005. godine 48% dece sa novootkrivenim dijabetesom imalo je DKA, a 10,4% ih je imalo tešku DKA [13]. U Srbiji se 41,5% dece sa novootkrivenim dijabetesom javlja sa DKA [14,15]. U većini studija nije dokazan uticaj pola na razvoj DKA kod dece u vreme postavljanja dijagnoze dijabetesa [7,16]. Jedino su u Finskoj dečaci pod većim rizikom [10].

Zaključak

Ovo je prvi izveštaj iz Crne Gore o učestalosti dijabetesne ketoacidoze kod dece sa novootkrivenim dijabetesom. Rezultati pokazuju da je prisutna tendencija smanjenja učestalosti što je najverovatnije rezultat edukacionih kampanja koje se sprovode u primarnoj zdravstvenoj zaštiti.

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ROBOT - ČLAN (RE)HABILITACIONOG TIMA

ROBOT – A MEMBER OF (RE)HABILITATION TEAM

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Sažetak

Uvod. U procesima rehabilitacije učestvuje čitav tim stručnjaka koji su angažovani tokom dužeg vremenskog perioda. **Razvoj robotike i primena u medicini.** Intenzivnim razvojem nauke i tehnike dizajniran je veći broj robota koji se koriste u terapijske svrhe i učestvuju u procesu rehabilitacije. **Robotika u medicinskoj rehabilitaciji.** Tokom duge istorije razvoja čovečanstva poznata su brojna idejna i tehnološka rešenja za konstrukciju robota. Primenom robota u medicinskoj rehabilitaciji moguće je sprovođenje rehabilitacije perifernog i centralnog motornog neurona, uz povećavanje motivacije pacijenta za dalji oporavak i uspešnost terapije. U radu su prikazana neka tehnološka rešenja za robotom potpomognutu rehabilitaciju pacijenata različitih uzrasnih grupa i neke mogućnosti primene u postupku lečenja. **Zaključak.** Uključivanje robota u standardne fizioterapijske protokole koji podrazumevaju veći broj ponavljanja, tačno doziranje, kvalitetno osmišljavanje i prilagođenost individualno svakom pacijentu dovode do značajnog napretka u rehabilitaciji pacijenata.

Ključne reči: Robotika; Rehabilitacija; Motorni neuron; Vežbanje; Oporavak funkcije

Summary

Introduction. The rehabilitation process involves a whole team of experts who participate in it over a long period of time. **Development of Robotics and its Application in Medicine.** The Intensive development of science and technology has made it possible to design a number of robots which are used for therapeutic purposes and participate in the rehabilitation process. **Robotics in Medical Rehabilitation.** During the long history of technological development of mankind, a number of conceptual and technological solutions for the construction of robots have been known. By using robots in medical rehabilitation it is possible to implement the rehabilitation of peripheral and central motor neurons by increasing the motivation of patients for further recovery and effectiveness of therapy. The paper presents some technological solutions for robot-assisted rehabilitation of patients of different age groups and some possibilities of its use in the treatment. **Conclusion.** Using robots in standard physiotherapy protocols that involve a number of repetitions, exact dosage, quality design and adaptability to each individual patient leads to the significant progress in the rehabilitation of patients.

Key words: Robotics; Rehabilitation; Motor Neurons; Exercise Therapy; Recovery of Function

Uvod

Rehabilitacija je „proces osposobljavanja osoba sa invaliditetom za povratak u društvo, odnosno u njihovu životnu i radnu sredinu, porodicu i društvo u širem smislu, kao i na radno mesto, pod, što je moguće, povoljnijim uslovima" [1]. U svakodnevnom radu lekara-fizijatara, pedijatara i svih onih koji se bave lečenjem dece sreće se i termin habilitacija. Habilitacija je „proces buđenja i aktiviranja sposobnosti, odnosno, funkcija koje nikada nisu bile razvijene, ili su postojale u rudimentarnom stepenu svog razvitka i to kod dece koja imaju neko nasledno, urođeno ili, u najranijem periodu, stečeno oštećenje ili povredu" [1]**.** U procesima (re)habilitacije učestvuje čitav tim stručnjaka tokom dužeg vremenskog perioda. U radu sa dečjom populacijom potrebni su kontinuirani i individualno koncipirani tretmani. Terapija pokretom (kineziterapija) bazični je deo rada sa pacijentima, ali se koriste i brojni modaliteti fizikalne terapije [2]. Intenzivnim razvojem tehnike, nastaje sve veći broj uređaja koji značajno smanjuju angažovanje terapeuta u aplikovanju određenih procedura, sve do razvoja robota, koji počinju da se koriste u terapijske svrhe i na dobrom su putu da postanu u budućnosti novi članovi (re)habilitacionog tima.

Razvoj robotike i primena u medicini

Tokom duge istorije tehnološkog razvoja čovečanstva poznata su brojna idejna i tehnička rešenja za konstrukciju robota. Sačuvane su skice i planovi

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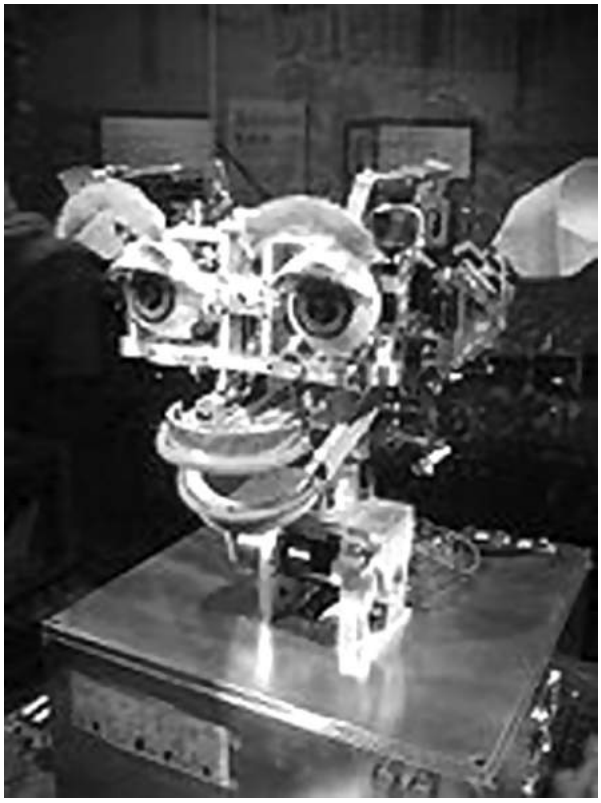
Skraćenice

R.U.R − *Rossumovi Univerzálni Roboti*
KASPAR − *Kinesics And Synchronisation in Personal Assistant Robotics*
MIME − *Mirror Image Movement Enabler*
FES − funkcionalna električna stimulacija
CIMT − *Constraint Induced Movement Therapy*

Leonarda da Vinčija za izradu androida [3]. Pojam „robot" prvi put se sreće u drami R.U.R (*Rossumovi Univerzálni Roboti*) Karela Čapeka iz 1920. godine [4]. Intenzivni razvoj robotike povezan je sa stvaranjem numerički kontrolisanih mašina od 1955. godine. Od sedamdesetih godina prošlog veka sprovedeno je više istraživačkih programa sa ciljem stvaranja različitih vrsta humanoidnih robota [5]. Robotika je grana tehnologije koja se bavi dizajnom, konstrukcijom i korišćenjem robota, a termin „robotika" prvi put upotrebio je pisac naučne fantastike Isak Asimov [6]. Razvoj robotike u bivšoj Jugoslaviji bio je vezan za Beogradsku školu robotike, kada je tim stručnjaka pod rukovodstvom akademika Miomira Vukobratovića proizveo uređaj namenjen kontroli stajanja, ali i hodanja kod pacijenata sa paraplegijom [7].

Robotika u medicinskoj (re)habilitaciji

Primena robota u medicinskoj (re)habilitaciji je u ekspanziji, sa velikim brojem idejnih rešenja i prototipova koji mogu da pomognu u određenim, ali ne i u svim fazama rehabilitacije pacijenata. Pri primeni robota u svakodnevnom radu postoje i brojne teškoće. Potrebno je savladati strah pacijenta, naročito ako su pacijenti deca [8]. Primenom ovih tehničkih rešenja može se povećati motivisanost pacijenata za dalji nastavak i uspešnost procesa (re)habilitacije [9]. Roboti koji se primenjuju u radu sa decom moraju biti niži od deteta, a spoljašnji izgled, odnosno dizajn, veoma je značajan. Deca stupaju u različite interakcije sa robotom, a uspešnost terapije zavisi od toga da li pacijent prihvata ovu vrstu interakcije ili ne. U radu sa decom najčešće se koriste roboti koji svojim izgledom podsećaju na mladunce različitih životinja, ali i humanoidni roboti. Robot *Paro*, dizajniran u vidu mladunca foke, ima posebne senzore koji reaguju na dodir otvaranjem i zatvaranjem očiju. U radu sa odraslim osobama najčešće se primenjuju humanoidni roboti, ali su i roboti koji podsećaju na praistorijske životinje (kao robot *Pleo*, dizajniran u formi dinosaurusa) bili prihvaćeni od starijih pacijenata [10]. Posebno dizajniran robot *Roball* podseća na malu lopticu, koristi se za podsticanje razvoja govora, motoričkih, intelektualnih i socijalnih veština kod dece uzrasta do 24 meseca [11]. U izradi robota velika se pažnja mora posvetiti njegovom licu, koje treba da bude izražajno i što sličnije ljudskom, sa velikim izražajnim očima, kapcima koji se pokreću, sa imitacijom pokretanja usana, uz funkciju pokretanja glave. Materijal od kojih se pravi robot mora biti indiferentan. U sastav-



Slika 1. Robot Kismet [13]
Fig 1. *Robot Kismet (13)*

ne delove robota spadaju i veštački pneumatski mišići, koji omogućuju veću elastičnost pri pokretanju pojedinih delova robota [12]. Spoljašnjost robota može biti obojena različitim bojama, što približnije realnim nijansama koje se sreću u prirodi. Postoje određene vrste robota koje su konstruisane tako da prikažu određeni izraz lica − robot *Kismet* **(Slika 1)** [13]. Ovaj tip robota se koristi u terapiji koja za cilj ima poboljšanje funkcije mimične muskulature (pacijent ponavlja i uvežbava podizanje obrva, zatvaranje očnih kapaka, osmehuje se).

Roboti se mogu koristiti i u terapiji različitih vidova poremećaja ponašanja kod dece. Autizam obuhvata široki spektar razvojnih poremećaja, koji ima različite manifestacije [14]. Karakterišu ga poremećaj socijalne interakcije, komunikacije i neuobičajeni obrasci pri dečjoj igri. Kod dece koja imaju autizam važno je postepeno učenje i razumevanje emocija i njihove facijalne ekspresije. Robot KASPAR (*Kinesics And Synchronisation in Personal Assistant Robotics*) može da prikaže izraz sreće, iznenađenja ili tuge, pri čemu postepeno uči dete da ih razlikuje i imitira u različitim socijalnim situacijama [15]. Robot KASPAR ima facijalnu ekspresiju sa manje složenosti nego pravo ljudsko lice, što pomaže deci sa autizmom da se bolje koncentrišu na lice robota [15]. Roboti koji se koriste u medicinskoj (re)habilitaciji mogu imati različite nivoe pokretljivosti. Mobilni roboti su opremljeni većim brojem internih i eksternih senzora, a kontrola ro-

bota je moguća pomoću kompjutera, ili je bežična kontrola [16]. Roboti koji se koriste za pozicioniranje i transfer bolesnika imaju najčešće točkove ili neku vrstu pokretnog stalka, platforme, sa različitim stepenima slobode pokreta između pojedinih delova konstrukcije [17].

Jedna od najčešćih indikacija za sprovođenje (re)habilitacionog tretmana su oštećenja centralnog motornog neurona, najčešće nakon cerebrovaskularnog inzulta. Ranom rehabilitacijom može se značajno uticati na povećanje stepena oporavka pacijenta, koristeći osobinu plasticiteta nervnog sistema [18]. U većem broju centara u poslednjih desetak godina razvijeno je više egzoskeletnih sistema za robotom potpomognutu rehabilitaciju gornjih ekstremiteta, od kojih su najpoznatiji MIT manus, MIME (*Mirror Image Movement Enabler*) i drugi [19]. Uz pomoć ovih sistema moguće je uvežbavanje pasivnih i aktivnih pokreta aficiranog ekstremiteta, ali i bimanuelnih aktivnosti [19]. Kineziterapija sa ciljem povećanja obima pokreta, naročito u palcu i kažiprstu može se sprovoditi i uz pomoć posebne elektronske senzorne rukavice ili pomoću aparata za funkcionalnu električnu stimulaciju (FES) [20]. Od pacijenta se traži da izvrši jednostavne zadatke, da podiže i spušta ili premešta predmete različitog oblika i veličine sa jednog mesta na drugo. Uvežbavaju se različiti hvatovi i jača se gruba mišićna snaga aficiranog ekstremiteta [21]. Na taj način se ubrzava proces oporavka, poboljšava se motorička kontrola šake, kao i fina motorika [22]. Kod nekih robota postoji mogućnost praćenja pokreta i na ekranu, kada pacijent ima i vizuelni fitbek izvedenog zadatka. Fizioterapeut nadgleda određenu aktivnost pacijenta u interakciji sa robotom i po potrebi se uključuje [23]. Kod dece sa cerebralnom paralizom koja imaju narušenu motoriku gornjih ekstremiteta robot potpomognutu terapija može omogućiti povećanje mišićne snage i obima pokreta, uz poboljšanje bimanuelnih aktivnosti [24]. Uz ovu terapiju može se koristiti i CIMT (*constraint induced movement therapy*), koja podrazumeva primenu ortoze na zdravoj ruci sa ciljem inhibicije aktivosti ove ruke, pri čemu se istovremeno potencira što veće korišćenje aficirane ruke [24]. Kod pacijenata sa paraplegijom mogu se koristiti posebne ortoze, koje u sebi sadrže veći broj senzora u različitim tačkama, tako da se na ekranu dobija posebna vrsta povratne vizuelne informacije, tokom boravka pacijenta na pokretnoj traci, uz suspenziju. Tokom tretmana postepeno se povećava zadata brzina, a analizira se poboljšanje preostalih motoričkih sposobnosti, brzina hoda, dužina i broj koraka, mišićna snaga i pokretljivost zglobova [25]. Uključivanje robota u standardne fizioterapijske protokole, koji podrazumevaju veliki broj ponavljanja, tačno doziranje, da su osmišljeni i prilagodljivi pacijentu, može da dovede do značajnog napretka u (re)habilitaciji. Smatra se da primena robota omogućava kraći vremenski period potreban za postizanje terapijskih ciljeva koji su zadati na početku tretmana [26]. Roboti koji imitiraju pokrete konja, mogu se koristiti za uvežbavanje balansa i pokretljivosti trupa, što su inače primarni efekti koji se dobijaju tokom hipoterapije ili terapijskog jahanja [27]. U procesu (re)habilitacije hoda mogu da se koriste različite vrste egzoskeletnih ortoza [28]. Ispred pacijenta se postavlja i ogledalo kako bi dobio povratnu informaciju o položaju svih segmenata tela u prostoru i tako poboljšala posturalna svesnost. Postupak se može ponavljati više puta tokom dana, tokom dužeg vremenskog perioda [29]. Primenom egzoskeleta za donje ekstremitete kao što je *Lokomat*, postiže se trening hoda koji je značajan deo tretmana u neurorehabilitaciji **(Slika 2)** [30].

Slika 2. Lokomat [30]
Fig. 2. *Locomat [30]*

Pokreti ortoza postavljenih na donje ekstremitete sinhronizovani su sa brzinom pokretne trake, štopacijentu daje osećaj sigurnosti, eliminiše strah, naročito kod pacijenata sa različitim neuromišićnim bolestima progresivnog toka [31]. Roboti koji učestvuju u (re)habilitaciji hoda imaju prednosti jer je u toku tretmana moguće sprovoditi veći broj koraka uvek istim ritmom i brzinom, što praktično nije moguće ako tretman sprovodi sam terapeut [29,31].

Zaključak

Prilagođavanje robota potrebama različitih vrsta terapija dovodi do veće primene robota u različitim tretmanima kako dece, tako i odraslih. Roboti su se pokazali kao značajan član (re)habilitacionog tima pogotovo u terapijama gde je neophodno puno ponavljanja ili dodatni stimulus kako bi pacijent što pravilnije i kvalitetnije obavio postavljeni zadatak. Sa napretkom tehnologije u budućnosti se očekuje smanjenje cene robota, a samim tim i veća dostupnost, tj. šira upotreba robota u različitim vrstama terapija. Na ovaj način roboti neće biti samo povremeni, već stalni članovi (re)habilitacionog tima.

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AUTOLOGI SERUM U TERAPIJI SUVOG OKA

AUTOLOGOUS SERUM IN TREATMENT OF DRY EYE

Gordana STANKOVIĆ BABIĆ i Sonja CEKIĆ

Sažetak

Uvod. Terapija suvog oka autologim serumom je jednostavna i jeftina terapijska mogućnost. Posebno je efikasna kod teških oblika suvog oka kao i hemijskih povreda oka, a opravdana zbog prisustva esencijalnih komponenti suza kojih nema u preparatima veštačkih suza. Cilj rada bio je analiza efekata terapije autologim serumom kod pacijenata sa suvim okom. **Materijal i metode.** Na Klinici za očne bolesti Kliničkog centra Niš praćen je efekat jednomesečne terapije suvog oka autologim serumom (korišćen uz preparate veštačkih suza) na 50 reumatoloških pacijenata (23 M : 27 Ž) starosti 26−65 godina. Analizirani su okularni diskomfor i vrednosti objektivnih parametara za procenu stanja prekornealnog suznog filma na početku lečenja i mesec dana kasnije (*Schirmer I*, *Tears Break Up Time* i *Rose bengal*). **Rezultati.** Statistički je značajno umanjenje subjektivnih tegoba kod ispitanika nakon terapije autologim serumom ($p < 0,05$), uz minimalno poboljšanje objektivnih testova za proveru kvaliteta suznog filma. **Diskusija i zaključak**. Primena autologog seruma u terapiji suvog oka treba da pruži boljitak pacijentima, da ublaži subjektivne tegobe i poboljša objektivne parametre za procenu suvog oka. Neophodna je adekvatna informisanost lekara i pacijenata, kao i pravilna trijaža potencijalnih korisnika ovog načina lečenja. Potrebna su dodatna ispitivanja terapijskog efekta autologog seruma (kao i seruma umbilikalne vrpce ili autologe plazme), paralelno kliničko, patohistološko ispitivanje i analiza efekata ovog vida terapije suvog oka.

Ključne reči: Sindrom suvog oka; Veštačke suze; Očne bolesti + terapija lekovima; Serum; Autologna transfuzija krvi

Summary

Introduction. The treatment of dry eye by autologous serum is a simple and inexpensive treatment option. It is particularly effective in severe forms of dry eye as well as for chemical eye injuries, and it is justified by the presence of essential tear components which are not found in preparations of artificial tears. The aim of this study was to analyze the effects of autologous serum therapy in the patients with dry eye. **Material and Methods.** We monitored the effect of one-month treatment of dry eye by autologous serum (used with artificial tear preparations) in 50 rheumatology patients (23 men and 27 women) aged 26-65 years at the Department of Ophthalmology, Clinical Center Nis. We analyzed ocular discomfort and the values of objective parameters for the evaluation of tear film at baseline and one month later (Schirmer I, Tears Break Up Time and Rose Bengal). **Results.** A statistically significant reduction of subjective complaints was found in the patients after the treatment by autologous serum ($p<0.05$), along with a minimal improvement of objective tests for checking the tear film quality. **Discussion and Conclusion.** The use of autologous serum in dry eye therapy should provide benefit to the patients, relieve symptoms and improve objective parameters for the evaluation of dry eye. Both doctors and patients should be adequately informed, and proper screening of potential users of this method should be done. Not only additional tests of therapeutic effect of autologous serum (as well as of umbilical cord serum or autologous plasma) are needed but also parallel clinical and histopathological examination and analysis of the effects of this type of treatment of dry eye.

Key words: Dry Eye Syndromes; Ophthalmic Solutions; Eye Diseases + drug therapy; Serum; Blood Transfusion, Autologous

Uvod

Suvo oko je multifaktorsko oboljenje suza i okularne površine, koje karakterišu simptomi diskomfora, smetnje vida, nestabilan suzni film i potencijalno oštećenje okularne površine. Nakon 2007. godine načinjen je značajan napredak u razumevanju patofiziologije suvog oka saznanjem da ovo oboljenje može biti udruženo sa povećanom osmolarnošću suznog filma i inflamacijom površine oka [1]. Poznavanje patofiziologije i dijagnostike suvog oka omogućava kvalitetniju i delotvorniju terapiju na dobrobit oko 15% celokupne populacije koja pati od nekog poremećaja ravnoteže suznog filma [2].

U osnovi terapije suvog oka su preparati veštačkih suza [3]. Široki etiološki spektar i individualnost pacijenata ne upućuju na univerzalno terapijsko rešenje suvog oka, te se preparati veštačkih suza kombinuju sa farmakološkim i nefarmakološkim modalitetima terapije prema preporukama stepenastog tretmana suvog oka grupe svetskih eksperata iz 2007. godine [4].

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Skraćenice

RA	– reumatoidni artritis
SLE	– sistemski lupus eritematozus
TBUT	– *Tears Break Up Time*
EGF	– epidermalni faktor rasta
aFGF i bFGF	– osnovni i kiseli fibroblast faktor rasta
PDGF	– iz trombocita izveden faktor rasta
GVHD	– *graft versus host disease* (bolest "kalem protiv domaćina")

Terapija suvog oka autologim serumom predstavlja jednostavnu, jeftinu terapijsku mogućnost, efikasnu kod teških oblika suvog oka i hemijskih povreda oka. Primena autologih seruma opravdana je zbog prisustva esencijalnih komponenti suza kojih nema u preparatima veštačkih suza poput faktora rasta, fibronektina, lizozima, imunoglobulina, a koji su zajedno sa vitaminima A i E odgovorni za proliferaciju, diferencijaciju i sazrevanje epitelnih ćelija okularne površine [4–11].

Cilj rada bio je analiza efekata terapije autologim serumom kod pacijenata sa suvim okom.

Materijal i metode

Na Klinici za očne bolesti Kliničkog centra Niš praćen je efekat jednomesečne terapije suvog oka autologim serumom. Ukupno je 50 pacijenata (23 M : 27 Ž) starosti 26–65 godina koristilo terapiju autologim serumom uz preparate veštačkih suza. Među ispitivanima, pored dijagoze suvo oko, pacijenti su imali i druge bolesti: reumatoidni artritis (RA) n = 35, sistemski lupus (SLE) n = 9, sistemsku sklerozu n =1, dermatomiozitis n = 2, polimiozitis n = 2 pacijenta i mešovitu bolest vezivnog tkiva n = 1 pacijent. Analizirani su okularni diskomfor izražen subjektivnim tegobama kod pacijenata i vrednosti objektivnih parametara za procenu stanja prekornealnog suznog filma na početku lečenja i mesec dana kasnije (*Schirmer I*, *Tears Break Up Time* (TBUT), *Rose bengal* test). Okularni diskomfor kao glavna karakteristika postojanja suvog oka, razmatran je kroz postojanje subjektivnih tegoba (osećaj suvoće, peckanja, bockanja, osećaj grebanja ili peska u očima, oči zalepljene sekretom i zatvorene ujutru, crvene i umorne oči, posebno pred kompjuterom, tokom čitanja ili vožnje) graduisan sa retko, često, stalno i kategorija bez subjektivnih tegoba. Ispitivani pacijenti imali su patološke vrednosti objektivnih testova za suvo oko (*Schirmer* I ≤10 mm/5, min; vreme pucanja prekornealnog suznog filma TBUT ≤10; *Rose bengal* ≥ 4 po Bijsterveldu).

Tabelarno prikazivanje podataka obavljeno je korišćenjem *MS Office Excel* programa, a proračuni su vršeni programom SPSS, verzija 15.0. Studentovim t-testom nezavisnih uzoraka, vršeno je testiranje statističke značajnosti razlike srednjih vrednosti iste grupe pacijenata pre i posle tretmana autologim serumom.

Za pripremu autologog seruma uzimano je venepunkcijom 40 ml krvi obolelog, koja je zatim centrifugirana 5 minuta na 1 500 obrtaja u Centralnoj biohemijskoj laboratoriji Kliničkog centra Niš. Dobijeni serum odvajan je u sterilnim uslovima i razblažen fiziološkim rastvorom (Sol. NaCl 0,9%) kao 20% rastvor u Galenskoj laboratoriji Niš; pakovan je u bočice od 5 ml sa ultravioletnom zaštitom i čuvan (čuvali su ga pacijenati) u frižideru na +4° C; korišćen je 4 puta dnevno, zajedno sa preparatom veštačkih suza koji je ukapavan 3 puta dnevno. Jedna bočica autologog seruma korišćena je u periodu od 7 dana, dok su ostale bile u zamrzivaču do upotrebe.

Rezultati

Okularni diskomfor i vrednosti pomenutih objektivnih parametara za procenu stanja prekornealnog suznog filma na početku lečenja i mesec dana kasnije prikazani su tabelarno **(tabele 1–4)**. Nakon terapije autologim serumom, utvrđeno je statistički značajno ublažavanje subjektivnih tegoba ($p < 0,05$) kod pacijenata sa suvim okom.

Kod sva tri objektivna testa za proveru kvaliteta suznog filma (*Schirmer I*, TBUT i *Rose bengal*) nalaz se popravio samo kod po jednog ispitanika. Kod *Rose bengal* testa, nalaz srednje prebojene okularne površine, posle terapije autologim serumom, postao je slabo pozitivan. Nalaz *Schirmer I* testa koji je pre terapije bio sa vrednostima 1–5 mm, nakon terapije autologim serumom je pripadao grupi nalaza sa vrednostima 6–10 mm. Kod jednog ispitanika sa vrednostima TBUT testa pre terapije ≤5 sekundi, nakon terapije autologim serumom popravljen je nalaz, što ga svrstava u povoljniju kategoriju sa vrednostima TBUT testa 6–10 sekundi.

Statistički je značajno umanjenje subjektivnih tegoba nakon terapije autologim serumom ($p < 0,05$), uz minimalno poboljšanje objektivnih testova za proveru kvaliteta suznog filma.

Tabela 1. Subjektivne tegobe kod ispitanika lečenih autologim serumom pre i posle terapije
Table 1. *Subjective complaints of patients treated by autologous serum before and after the treatment*

Subjektivne tegobe/*Subjective complaints*	Pre th/*Before treatment*		Posle th/*After treatment*	
Nema/*None*	11	10%	14	60%
Retko/*Rarely*	14	40%	13	40%
Često/*Often*	13	30%	12	0%
Stalno/*Constantly*	12	20%	11	0%
Ukupno/*Total*	50	100%	50	100%

Tabela 2. Razultati *Schirmer* I testa kod ispitanika lečenih autologim serumom pre i posle terapije
Table 2. *Schrimer I test results in patients treated by autologous serum before and after the treatment*

Schirmer I	Pre th/*Before treatment*		Posle th/*After treatment*	
1−5 mm	24	40%	23	30%
6−10 mm	26	60%	27	70%
Ukupno/*Total*	50	100%	50	100%

Tabela 3. Vreme pucanja prekornealnog suznog filma (TBUT) kod ispitanika lečenih autologim serumom pre i posle terapije
Table 3. *Tear Break-Up Time (TBUT) in patients treated by autologous serum before and after treatment*

TBUT/*TBUT*	Pre th/*Before treatment*		Posle th/*After treatment*	
≤ 5 s	24	40%	23	30%
6−10 s	26	60%	27	70%
Ukupno	50	100%	50	100%

Tabela 4. *Rose bengal* test kod ispitanika lečenih autologim serumom pre i posle terapije
Table 4. *Rose bengal test in patients treated by autologous serum before and after treatment*

Rose bengal	Pre th/*Before treatment*		Posle th/*After treatment*	
Slabo/*Poor*	27	70%	28	80%
Srednje/*Medium*	12	20%	11	10%
Konfluentna polja/*Confluent fields*	11	10%	11	10%
Ukupno/*Total*	50	100%	50	100%

Diskusija

Mogućnost lečenja suvog oka autologim serumom prvi pominju Fox i saradnici 1984. godine [8]. S obzirom da suze nastaju modifikacijom sastava krvnog seruma u epitelu sekretorne jedinice suzne žlezde [12−14], biohemijske karakteristike suza i seruma su slične i ovaj način lečenja suvog oka ima opravdanja.

I serum i suze sadrže vitamin A, epidermalni faktor rasta (EGF), osnovni i kiseli fibroblast faktor rasta (bFGF i aFGF), iz trombocita izveden faktor rasta (PDGF), insulin tip-1 faktor rasta, supstanciju P, laktoferin, lizozime [15,16]. Retinol je 1 000 puta koncentrovaniji u serumu u odnosu na suze, a u 20% autologom serumu je najbolje koncentracije, što je značajno za oboljenja oka uzrokovana hipovitaminozom vitamina A [17]. Faktori rasta (EGF i transformišući faktor rasta -TGF β) ubrzavaju proliferaciju kornealnog epitela anti-apoptotičnim svojstvima, kontrolišu epitelijalnu proliferaciju, održavaju ćelije u nediferentovanom stanju, dok je supstancija P značajna za migraciju kornealnih epitelijalnih ćelija [15,16]. Humani serum stimuliše migraciju kornealnih fibroblasta, proliferaciju i aktivnost matriks metaloproteinaza [15], a antiproteaza poput β-2 makroglobulina, inhibira kolagenaze rožnjače što je značajno kod hemijskih povreda oka bazama [15,16].

Lipidi u serumu mogu da zamene lipidni sloj suza, dok proteini u serumu koji su inače prisutni u visokoj koncentraciji, stabilizuju suzni film (prealbumini) i štite degradaciju značajnih citokina (albumin i globulini) [15].

Da autologi serum poboljšava stanje konjunktive kod pacijenata sa suvim okom pokazuju rezultati impresione citologije konjunktive i objektivni testovi bojenja očne površine u kliničkim studijama [15].

Indikacije za primenu autologih seruma bile bi: suvo oko u Sjegrenovom sindromu (SS), keratokonjunktivitis sika (KCS), perzistenti epitelijalni defekti gde konvencionalna terapija nije uspešna (deficit stem-ćelija), kod postherpetičnih ulkusa kod obolelih od dijabetesa zbog neurotropnih problema, nakon rekonstrukcije okularne površine, transplantacije rožnjače, kod Stivens-Džonsonovog sindroma, cikatricijalnog pemfigoida, kod opekotina bazama koje ne reaguju na konvencionalni način lečenja, za terapiju tzv. gornjeg limbičnog keratokonjunktivitisa (SLK), suvog oka zbog bolesti „kalem protiv domaćina" (engl. *graft versus host desease* − GVHD), a preporučuje se upotreba autologog seruma (0,1 ml) i nakon hirurškog tretmana zaravnjenja makularnih haloa [15].

Kontraindikacije za primenu autologog seruma su perzistentni epitelijalni defekti kod obolelih sa reumatoidnim artritisom, raniji herpes simpleks

keratitis, Morenov ulkus, bakterijski keratitis, hepatitis i HIV [15].

Neželjeni efekti terapije autologim serumom su mogući, ali retki, odnose se na depozite imunokompleksa u slučaju postojanja perzistentnih epitelijalnih defekata kod obolelih sa reumatoidnim artritisom ili ranije virusne infekcije rožnjače, zbog postojanja autoantitela u serumu protiv reuma faktora i herpes virus simpleks antigena. Infektivni keratitis i konjunktivitis su mogući ukoliko je autologi serum infektivan [15].

Prednosti terapije suvog oka autologim serumom su sastav, stabilnost preparata ukoliko se pravilno pripremi, čuva, koristi i minimalni neželjeni efekti.

Autologi serum se priprema prema preskripciji lekara u saradnji sa farmaceutom ili ga priprema lekar sam. Pacijent pre početka terapije autologim serumom mora biti upoznat sa planiranom terapijom kao vidom alternativnog lečenja suvog oka, eventualnim rizicima (bakterijska kontaminacija), načinom čuvanja i aplikovanja preparata [8].

Krv se uzima venepunkcijom u pravilno obeležene bočice (datum uzimanja, generalije). Mora biti poštovana procedura pripreme počev od centrifugiranja, preko pripreme i čuvanja dobijenog rastvora. Autologi serum je bez konzervansa i sa visokim je rizikom od kontaminacije u toku pripreme (ređe) i od samog korisnika ovog medicinskog pripravka [16]. Prema saopštenjima iz literature, nije bilo kontaminacije autologog seruma do 12 nedelja ukoliko je pravilno pripremljen i čuvan [15].

Za pripremu autologog seruma ne sme se uzimati krv obolelog kod sumnje na septikemiju, pacijenata pozitivnih na HIV, virusni hepatis B i C, sifilis zbog rizika od indukovane infekcije [15].

Autologi serum se čuva u tamnim bočicama i na tamnom mestu zbog razgradnje vitamina A. Bočica se koristi 7 dana, a čuva u frižideru na +4˚ C, dok je ostala količina autologog seruma dobijena jednom venepunkcijom u zamrzivaču do upotrebe [8, 15]. Koncentracija faktora rasta, vitamina A, fibronektina u 100% i 20% autologom serumu je stalna ukoliko se čuva na temperaturi od +4˚ C mesec dana ili na –20˚ C 3 meseca [8,15,16].

Radi se na tehnološkom poboljšanju autologog seruma, razmišlja o liofilizaciji produkta slično pripremi vakcina kojom bi se dobilo na stabilnosti pripravka, o dodatku biopolimera za regeneraciju rožnjače i specifičnih mukozno-adhezivnih komponenti, kojima bi se povećalo vreme kontakta sa kornealnom površinom. Time bi se u bliskoj budućnosti mogli da formulišu rastvori autologog seruma prema specifičnim potrebama pacijenata [16].

Primena autologog seruma u terapiji suvog oka treba pacijentima da pruži poboljšanje, da ublaži subjektivne tegobe i popravi objektivne parametre za procenu suvog oka. Primenu autologih seruma u našoj grupi pacijenata karakteriše smanjenje okularnog diskomfora kod obolelih koje pokazuje statističku značajnost, poboljšanje vrednosti objektivnih testova za kvalitet suznog filma (*Schirmer I*, TBUT, *Rose bengal* testa) bez statistički značajne razlike pre i posle terapijom autologim serumom. Smatramo da je već i samo smanjenje okularnog diskomfora razlog za terapiju suvog oka autologim serumom.

Neophodna je svakako adekvatna informisanost lekara i pacijenata, kao i pravilna trijaža potencijalnih korisnika ovog načina lečenja suvog oka.

Preparatima veštačkih suza u kombinaciji sa pravovremenom antiinflamatornom terapijom kontrolišu se simptomi bolesti suvog oka, usporava tok prirodne progresije bolesti i sprečavaju teške komplikacije. Kombinacijom navedenih terapeutskih mogućnosti, treba da se ostvari osnovni cilj prevencije progresije suvog oka – prekid ciklusa stimulacije površine oka/imunosistema. Individualnost pacijenata i široka paleta etioloških faktora suvog oka upućuje nas na izbor i odgovarajući redosled ponuđenih terapijskih opcija [18].

U terapiji teške forme suvog oka u Sjegrenovom sindromu, perzistentih epitelnih defekata, neurotrofne keratopatije, gornjeg limbičnog keratitisa, rekurentnih kornealnih erozija, bolesti „kalem protiv domaćina" može se koristiti i serum umbilikalne vrpce. Smatra se čak mnogo efikasnijom terapijom u odnosu na terapiju autologim serumom jer smanjuje tegobe suvog oka, doprinosi poboljšanju keratoepiteliopatije u teškoj formi suvog oka i povećava gustinu peharastih ćelija u Sjegrenovom sindromu [19−21]. Saopšteni su i pokušaji terapije autologom plazmom bogatom krvnim pločicama, koja se pokazala veoma efikasnom u regeneraciji tkiva i zarastanju rana uopšte, pa i u tretmanu pacijenata sa signifikantno suvim okom [22].

S obzirom da biološka terapija zauzima sve opravdanije mesto u oftalmologiji, potrebna su dodatna ispitivanja terapijskog efekta autologog seruma (kao i seruma umbilikalne vrpce ili autologe plazme), paralelno kliničko, patohistološko ispitivanje i analiza efekata ovog vida terapije suvog oka.

Zaključak

Prikazana je mogućnost terapije suvog oka autologim serumom. Statistički je značajno umanjenje subjektivnih tegoba u grupi ispitanika lečenih autologim serumom ($p < 0,05$), uz minimalno poboljšanje objektivnih testova za proveru kvaliteta suznog filma. Primena autologog seruma u terapiji suvog oka treba da pruži boljitak pacijentima, da ublaži subjektivne tegobe i poboljša objektivne parametre za procenu suvog oka.

Adekvatna informisanost lekara i pacijenata je neophodna, kao i pravilna trijaža potencijalnih korisnika ovog načina lečenja.

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VANBOLNIČKI MORBIDITET STANOVNIŠTVA ŠUMADIJSKOG OKRUGA

OUT-HOSPITAL MORBIDITY OF POPULATION IN SHUMADIA DISTRICT

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Sažetak

Uvod/cilj. Cilj rada je analiza vanbolničkog morbiditeta stanovništva Šumadijskog okruga i identifikacija prioritetnih zdravstvenih problema. **Materijal i metode.** Kao izvor podataka korišćeni su izveštaji o oboljenjima, stanjima i povredama službi opšte medicine, službi za zdravstvenu zaštitu predškolske i školske dece i službi za zdravstvenu zaštitu žena domova zdravlja Šumadijskog okruga. Urađena je analiza vanbolničkog morbiditeta za period 1999−2008. godine. **Rezultati.** Vodeće mesto u strukturi morbiditeta u službama opšte medicine na teritoriji Šumadijskog okruga zauzimaju bolesti sistema za krvotok sa 22,4%. U morbiditetu predškolske i školske dece i omladine najzastupljenija je grupa bolesti sistema za disanje. U službama za zdravstvenu zaštitu žena više od polovine ukupnog morbiditeta (63,9%) čini grupa bolesti mokraćno-polnog sistema. **Zaključak.** U strukturi morbiditeta stanovništva Šumadijskog okruga dominiraju masovne nezarazne bolesti te je neophodno intenziviranje promotivno-preventivnih mera i aktivnosti sa ciljem unapređenja zdravlja stanovništva i rešavanja prioritetnih problema.

Ključne reči: Morbiditet; Kardiovaskularna oboljenja; Respiratorna oboljenja; Genitourinarna oboljenja; Predškolsko dete; Dete; Odrasli; Muško; Žensko; Primarna zdravstvena zaštita

Summary

Introduction. The aim of this paper was to analyze out-hospital morbidity of population in the district of Shumadia and to identify the priority health problems. **Material and Methods.** The data source were the Reports on diseases, conditions and injuries provided by Department of General Medicine, Department of Preschool and School children Health Care and Department of Women's Health Care at Health Care Centres in the district of Shumadia for the period from 1999 to 2008. **Results.** Cardiovascular diseases account for 22.4% of morbidity in the district of Shumadia, thus taking the leading place in the morbidity structure according to Departments of General Medicine. However, pulmonary diseases are the most frequent ones in pre-school and school children and diseases of genitourinary system in females account for more than a half (63.9%) of the total morbidity in the Departments of Women's Health Care. **Conclusion.** As the mass non-contagious diseases are dominating in the morbidity and mortality structure of population in the district of Shumadia, it is necessary to intensify promotional-preventive measures and activities in order to improve the health status of the population and to solve the priority health problems.

Key words: Morbidity; Cardiovascular Diseases; Respiratory Tract Diseases; Urologic Diseases; Child, Preschool; Child; Adult; Male; Female; Primary Health Care

Uvod

Zdravstveno stanje stanovništva predstavlja važan pokazatelj potencijala jednog društva kao i funkcionisanje zdravstvene zaštite i organizacije zdravstvene službe [1].

Zdravstveno stanje stanovništva predstavlja osnovu za objektivnu identifikaciju prioriteta, stimulisanje akcija ili preispitivanje ciljeva zdravstvene politike, strategija i tehnologija u zdravstvenoj zaštiti. Predstavlja opis i/ili merenje zdravlja pojedinca, grupe ili celokupne populacije prema prihvaćenim standardima uz pomoć zdravstvenih indikatora ili, preciznije, to je stanje zdravlja osobe ili stanovništva procenjeno u odnosu na: opšti morbiditet, morbiditet od određenih bolesti, invalidnost, antropometriju, mere mortaliteta, pokazatelje funkcionalnog statusa i kvaliteta života. To je složena procedura dobijanja slike zdravlja stanovništva korišćenjem indikatora [2].

Ciljevi procene zdravstvenog stanja stanovništva jesu unapređenje zdravstvenog stanja stanovništva, identifikovanje prioritetnih zdravstvenih problema, praćenje promena zdravstvenog stanja tokom vremena, uočavanje i analiza razlika između različitih teritorija ili populacionih grupa [3].

Analiza zdravstvenog stanja do kraja 19. veka bazirala se, gotovo isključivo, na podacima o mortalitetu, dok se tokom 20. veka uvode i pokazatelji morbiditeta, kojima se prati ne samo obolevanje stanovništva već i njegove posledice [4].

S porastom hroničnih degenerativnih oboljenja, strategija procene zdravlja obuhvata i pokazatelje vremena izgubljenog za vreme nesposobnosti i invalidnosti. Za sadašnji period procene zdravstvenog stanja karakteristično je da se u proces

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Tabela 1. Registrovana oboljenja u primarnoj zdravstvenoj zaštiti dece, na teritoriji Šumadijskog okruga, 1999–2008.
Table 1. *Reported diseases in primary care of children on the territory of Shumadia District, 1999-2008*

Godina *Year*	Ukupan broj oboljenja *Total number of cases*	Stopa obolevanja na 1 000 stanovnika 0–6 godina *Incidence rate per 1.000 inhabitants aged 0-6 years*	Procentualno učešće najčešće registrovanih oboljenja u ukupnom broju oboljenja *Percentage of the most frequently reported diseases in the total number of diseases*					
			Bolesti sistema za disanje *Diseases of the respiratory system*	Bolesti uva i mastoidnog nastavka *Diseases of the ear and mastoid process*	Faktori koji utiču na zdravstveno stanje i kontakt sa zdravstvenom službom *Factors influencing health status and contact with health services*	Bolesti kože i potkožnog tkiva *Diseases of the skin and subcutaneous tissue*	Zarazne i parazitarne bolesti *Certain infectious and parasitic diseases*	Bolesti sistema za varenje *Diseases of the digestive system*
1999.	102 930	5 085,7	76,2	4,7	4,1	4,5	2,4	2,1
2000.	117 469	5 804,1	72,7	4,8	4,5	4,8	3,7	2,5
2001.	124 306	6 141,9	73,8	4,2	5,4	4,2	3,2	2,3
2002.	118 246	5 842,5	71,9	4,2	5,4	4,8	3,2	3,1
2003.	110165	5 443,2	72,1	4,8	5,5	4,6	3	2,4
2004.	109 295	5 358,6	67,2	4,4	6,8	5,2	4,5	3,5
2005.	105 957	5 235,2	68,6	4,3	6,8	5,1	3,8	2,9
2006.	122 639	6 059,5	61,4	4,4	13,6	4,8	4,1	2,8
2007.	123 634	6 108,7	65,6	4,9	8,4	5,3	3,3	3
2008.	134 952	6 667,9	64,5	5,3	8,8	4,7	3,6	3,3

procene uključuju i psihička i socijalna komponenta zdravlja a ne samo njegov fizički aspekt [3].

Morbiditet (obolevanje) direktni je pokazatelj zdravstvenog stanja stanovništva [2,4].

Pouzdanost ovog pokazatelja smanjena je činjenicom da se teže prikupljaju podaci i nizom drugih nepravilnosti u vezi sa prikupljanjem. Kao jedinice posmatranja uzimaju se obolelo lice, oboljenje i epizode oboljenja [5].

U našoj zemlji, morbiditetna statistika registruje oboljenje (a ne obolelo lice), pri čemu jedno lice može bolovati od više bolesti istovremeno i više puta u toku godine [6].

Cilj analize vanbolničkog morbiditeta stanovništv Šumadijskog okruga jeste identifikacija prioritetnih zdravstvenih problema kako bi se preduzele odgovarajuće mere za njihovo rešavanje.

Materijal i metode

Kao izvor podataka korišćeni su izveštaji o oboljenjima, stanjima i povredama službi opšte medicine, službi za zdravstvenu zaštitu predškolske i školske dece i službi za zdravstvenu zaštitu žena domova zdravlja Šumadijskog okruga. Urađena je analiza vanbolničkog morbiditeta za period 1999–2008. godine.

Rezultati

U službama za zdravstvenu zaštitu predškolske dece u Šumadijskom okrugu ukupan broj registrovanih oboljenja i stanja iznosio je 2008. godine 134 952, a stopa obolevanja bila je 6 667,9 na 1 000 dece uzrasta 0–6 godina (ili 6,7 po detetu), što je za 31,1% viša stopa nego ona koja je zabeležena 1999. godine kada je iznosila 5 085,7 na 1 000 dece uzrasta 0–6 godina (ili 5 po detetu). U strukturi registrovanog vanbolničkog morbiditeta kod dece predškolskog uzrasta, na prvom mestu bile su bolesti sistema za disanje (X grupa MKB-10) sa stalnim padom učešća u morbiditetu u toku posmatranog perioda sa 76% u 1999. godini na 64% u 2008. godini; zarazne i parazitarne bolesti (I grupa MKB-10) sa porastom učešća od 2,1% u 1999. na 3,3% u 2008. godini, bolesti uva i mastoidnog nastavka (VIII grupa MKB-10) sa skoro konstantnim učešćem od 4%, bolesti kože i potkožnog tkiva (XII grupa MKB-10) sa konstantnim učešćem oko 5% i bolesti sistema za varenje (XI grupa MKB-10) koje se od 2000. godine usled uvođenja kategorije faktori koji utiču na kontakt sa zdravstvenom službom (XXI grupa MKB-10), ne nalaze u prvih pet najčešćih grupa bolesti **(Tabela 1)**.

U Šumadijskom okrugu ukupan broj evidentiranih oboljenja i stanja školske dece u 2008. godini iznosio je 127 360 ili 3 oboljenja po jednom školskom detetu. Stopa obolevanja iznosila je 3 048 na 1 000 dece školskog uzrasta. U 2008. godini u strukturi morbiditeta na prvom mestu nalaze se bolesti sistema za disanje (grupa X MKB-10) sa učešćem od 52,6%. Na drugom mestu nalaze se faktori koji utiču na zdravstveno stanje i kontakt sa zdravstvenom službom (grupa XXI MKB-10) sa 14,2%, zatim slede bolesti kože i potkožnog tkiva (grupa XII MKB-10) sa 5,9%, povrede, trovanja i posledice delovanja spoljnih faktora (grupa XIX MKB-10) sa 4,2% i zarazne i parazitarne bolesti (grupa I MKB-10) sa 2,5%. Pobrojanih pet grupa

Tabela 2. Oboljenja registrovana u primarnoj zdravstvenoj zaštiti školske dece, na teritoriji Šumadijskog okruga, 1999–2008.
Table 2. *Reported diseases in primary health care of school children on the territory of Shumadia district, 1999-2008.*

Godina *Year*	Ukupan broj oboljenja *Total number of cases*	Stopa obolevanja na 1 000 stanovnika 7–19 godina *Incidence rate per 1,000 inhabitants aged 7-19 years*	Procentualno učešće najčešće registrovanih oboljenja u ukupnom broju oboljenja *Percentage of the most frequently reported diseases in the total number of diseases*				
			Bolesti sistema za disanje *Diseases of the respiratory system*	Faktori koji utiču na zdravstveno stanje i kontakt sa zdravstvenom službom *Factors influencing health status and contact with health services*	Zarazne i parazitarne bolesti *Certain infectious and parasitic diseases*	Bolesti kože i potkožnog tkiva *Diseases of the skin and subcutaneous tissue*	Povrede, trovanja i posledice delovanja spoljnih faktora *Injury, poisoning and certain other consequences of external causes*
1999.	118 337	2 832	71,9	4,1	1,8	4,2	3,2
2000.	127 512	3 051	67,8	3,7	1,4	5,0	2,7
2001.	148 600	3 556	68,8	3,9	1,2	4,8	2,3
2002.	127 531	3 052	65,5	5,0	1,6	5,3	3,4
2003.	107 578	2 575	66,6	5,7	1,9	5,2	3,8
2004.	99 464	2 380	61,4	7,2	2,7	6	4,1
2005.	83 828	2 006	61,6	7,6	2,5	6	4,1
2006.	96 402	2 307	55,5	11,6	2,7	5,8	4,5
2007.	111 536	2 670	54,3	10,8	2,7	6,2	4,6
2008.	127 360	3 048	52,6	14,2	2,5	5,9	4,8

bolesti čine 82% svih oboljenja i stanja u morbiditetu školske dece u 2008. godini **(Tabela 2)**.

U službama opšte medicine na teritoriji Okruga u 2008. godini registrovano je ukupno 395 262 oboljenja i stanja sa stopom obolevanja od 1 678 na 1 000 stanovnika. To predstavlja povećanje u odnosu na 1999. godinu kada je stopa morbiditeta iznosila 642 na 1 000 stanovnika. Kod odraslog stanovništva u Šumadijskom okrugu dominirale su bolesti sistema za disanje sve do 2006. godine, kada predominaciju preuzimaju bolesti sistema krvotoka. Slede bolesti mišićno-koštanog sistema i vezivnog tkiva **(Tabela 3)**.

U Šumadijskom okrugu, broj registrovanih oboljenja u službama za zdravstvenu zaštitu žena domova zdravlja u periodu 1999–2008. godine kretao se od 33 613 u 1999. godini do 54 538 koliko je iznosio 2008. godine. Stopa obolevanja 1999. godine bila je 260 na 1 000, a 2008. godine 423 na 1 000 žena. U ukupnom morbiditetu, pet najčešćih grupa oboljenja bile su: bolesti mokraćno-polnog sistema koje su dominirale u strukturi morbiditeta sa preko 58%, faktori koji utiču na kontakt sa zdravstvenom službom sa učešćem od 25,8% u 1999. do 25,9% u 2008. godini, trudnoća, rađanje i babinje sa učešćem 7,2% u 1999. godini i stalnim padom učešća do 4,3% u 2008. godini, zarazne i parazitarne bolesti sa učešćem od 4% i stalnim padom do 2008. godine sa učešćem od 1,4% i tumori sa učešćem oko 3% u celom posmatranom periodu **(Tabela 4)**.

Diskusija

Rezultati našeg istraživanja pokazuju da je na teritoriji Šumadijskog okruga stopa obolevanja na 1 000 dece uzrasta 0–6 godina viša nego u Republici Srbiji za 25%. U Srbiji u 2007. godini stopa obolevanja na 1 000 dece uzrasta 0–6 godina iznosila je 5 308,8 [7].

U službi za zdravstvenu zaštitu predškolske dece na teritoriji Šumadijskog okruga u 2008. godini, gotovo dve trećine (64%) svih registrovanih dijagnoza su iz grupe bolesti sistema za disanje, što je slučaj i sa podacima za teritoriju Centralne Srbije za 2007. godinu gde takođe vodeće mesto zauzimaju bolesti sistema za disanje (64,28%) [8].

Ukupan broj evidentiranih oboljenja i stanja školske dece u Republici Srbiji u 2007. godini iznosio je 2,3 oboljenja po jednom školskom detetu [7], a na teritoriji Šumadijskog okruga za trećinu više.

Poredeći rezultate dobijene našim istraživanjem sa rezultatima za Republiku Srbiju i Vojvodinu za 2006. godinu, možemo reći da je u strukturi morbiditeta dece školskog uzrasta najzastupljenija grupa bolesti sistema za disanje. Bolesti sistema za disanje či- ne više od polovine (52,6%) ukupnog morbiditeta školske dece i omladine na teritoriji Šumadijskog okruga, a 60,13% od ukupnog morbiditeta na teritoriji Centralne Srbije i 44,45% na teritoriji Vojvodine [8].

U Republici Srbiji stopa obolevanja kod odraslog stanovništva u 2007. godini iznosila je 1 473,7 na 1 000 stanovnika, što znači da je svaki odrasli

Tabela 3. Registrovana oboljenja u primarnoj zdravstvenoj zaštiti odraslog stanovništva, na teritoriji Šumadijskog okruga, 1999–2008.
Table 3. *Reporteddiseases in primary health care in adult population on the territory of Shumadia District, 1999-2008*

Godina *Year*	Ukupan broj oboljenja *Total number of cases*	Stopa obolevanja na 1 000 odraslih stanovnika *Incidence rate per 1.000 adult inhabitants*	Procentualno učešće najčešće registrovanih oboljenja u ukupnom broju oboljenja *The percentage of the most common registered diseases in the total number of diseases*				
			Bolesti sistema krvotoka *Diseases of the circulatory system*	Bolesti sistema za disanje *Diseases of the respiratory system*	Bolesti sistema za varenje *Diseases of the digestive system*	Bolesti mokraćno-polnog sistema *Diseases of the genitourinary system*	Bolesti mišićno-koštanog sistema i vezivnog tkiva *Diseases of the musculoskeletal system and connective tissue*
1999.	149 730	642	17,8	30	5,2	6,2	9,4
2000.	176 140	755	18	30,8	5,6	6	10,6
2001.	198 475	851	20,6	35,2	6,5	7,6	9,9
2002.	188 716	801	18,1	30,3	5,9	6,3	10
2003.	211 805	899	18,5	27,2	6	6,6	10,1
2004.	207 526	881	19,4	28,1	5,2	6,5	10,4
2005.	229 097	973	21,4	26	5,1	6,4	9,9
2006.	271 943	1 154	20,4	21,7	5,6	7,2	9,6
2007.	311 502	1 323	22,4	20	5,4	6,6	9
2008.	395 262	1 678	22,4	18,8	6,6	6,5	5,7

stanovnik Republike Srbije imao nešto manje od 1,5 oboljenja [7].

U vanbolničkom morbiditetu odraslog stanovništva na teritoriji Republike Srbije u 2007. godini registrovano je ukupno 8 543 792 oboljenja i stanja. U strukturi razbolevanja odraslog stanovništva u 2007. godini dominiraju bolesti sistema za disanje, zatim bolesti sistema krvotoka i bolesti mišićno-ko-

Tabela 4. Registrovana oboljenja u primarnoj zdravstvenoj zaštiti žena, na teritoriji Šumadijskog okruga, 1999–2008.
Table 4. *Reported diseases in primary health care for women on the territory of Shumadia District, 1999-2008*

Godina *Year*	Ukupan broj oboljenja *Total number of cases*	Stopa obolevanja na 1 000 žena starih 15+ *Incidence rate per 1.000 women aged 15 +*	Procentualno učešće najčešće registrovanih oboljenja u ukupnom broju oboljenja *Percentage of the most frequently reported diseases in the total number of diseases*				
			Bolesti mokraćno-polnog sistema *Diseases of the genitourinary system*	Faktori koji utiču na zdravstveno stanje i kontakt sa zdravstvenom službom *Factors influencing health status and contact with health services*	Trudnoća, rađanje i babinje *Pregnancy, childbirth and the puerperium*	Zarazne i parazitarne bolesti *Certain infectious and parasitic diseases*	Tumori *Neoplasms*
1999.	33 613	260	58,5	25,8	7,2	4	3,3
2000.	43 910	340	59,5	25,5	6,2	3,8	3,4
2001.	38 302	297	65,7	20	5,5	3,6	3,7
2002.	35 315	274	66,4	20,7	5	3	3,5
2003.	29 823	231	60,2	27,3	6,2	1,8	3,2
2004.	31 837	247	59,8	28,5	5,7	2,1	3,1
2005.	32 234	250	58,4	29,7	5,2	2,7	3,3
2006.	27 353	213	60,8	26,1	4,9	3,1	3,8
2007.	31 654	245	60	29,5	3,7	2,1	3
2008.	54 538	423	63,9	25,9	4,3	1,4	3

štanog sistema i vezivnog tkiva. Kada je reč o pojedinačnim oboljenjima, najčešće su registrovani povišen krvni pritisak nepoznatog porekla (MKB-10: I10), sa učešćem od 11,8% u ukupnom morbiditetu u 2007. godini, akutno zapaljenje ždrela i akutno zapaljenje krajnika (MKB-10: J02 i MKB-10: J03) sa 10,7% i druga oboljenja leđa (MKB-10: M40-M49 i M53-M54) sa 5,88% [7].

Kod odraslog stanovništva u Šumadijskom okrugu stope obolevanja su pokazivale porast tokom čitavog posmatranog perioda, a dominirale su bolesti sistema za disanje sve do 2006. godine, kada predominaciju preuzimaju bolesti sistema krvotoka sa zastupljenošću od 22,4% u poslednjoj godini posmatranja.

I u Republici Srbiji kao i u Šumadijskom okrugu broj registrovanih oboljenja u službama za zdravstvenu zaštitu žena u domovima zdravlja je rastao, a samim tim i stope morbiditeta [7].

Bolesti mokraćno-polnog sistema koje su dominirale u strukturi morbiditeta sa preko 50% učešća nalaze se na prvom mestu u vanbolničkom morbiditetu žena u Republici Srbiji u 2007. godini [7], dok podaci dobijeni za teritoriju Šumadijskog okruga za 2008. godinu pokazuju da su ove bolesti zastupljene u nešto većem procentu (63,9%).

Rezultati slični našim, zabeleženi su i u zemljama u okruženju. U vanbolničkom morbididtetu Republike Hrvatske za 2006. godinu, u službi opšte medicine najzastupljenije su bolesti sistema za disanje (21% ukupnog morbiditeta), slede bolesti sistema krvotoka sa 12,7% i bolesti mišićno-koštanog sistema i vezivnog tkiva sa zastupljenošću od 10,8%. Kod predškolske dece najzastupljenije su bolesti sistema za disanje (51,2%), a slede zarazne i parazitarne bolesti sa učestalošću od 8,9%. Isti je redosled vodećih uzroka obolevanja i u školskom uzrastu: bolesti sistema za disanje čine 51,9%, a zarazne i parazitarne bolesti 9,3% ukupnog morbiditeta ove dobne grupe. Najčešće grupe bolesti i stanja zbog kojih su žene dolazile u ginekološku ordinaciju i koristile usluge primarne zdravstvene zaštite žena u 2006. godini su, kao i poslednjih nekoliko godina, gotovo iste. To su bolesti mokraćnog i polnog sistema s učešćem od 48,7%; faktori koji utiču na stanje zdravlja i kontakt sa zdravstvenom službom 25,9%; zarazne i parazitarne bolesti 12,1%; trudnoća, porođaj i babinje 5,6% [9].

U Crnoj Gori u 2006. godini, vodeće mesto u strukturi morbiditeta u vanbolničkim službama zauzimaju bolesti sistema za disanje (47,22%), slede faktori koji utiču na zdravstveno stanje i kontakt sa zdravstvenom službom (11,46%) i bolesti mokraćno-polnog sistema sa zastupljenošću od 6,85%, dok su bolesti sistema krvotoka na četvrtom mestu (6,23%) [10].

Zaključak

Na teritoriji Šumadijskog okruga vodeći uzrok obolevanja kod dece predškolskog i školskog uzrasta su bolesti sistema za disanje. U populaciji žena najzastupljenije su bolesti mokraćno-polnog sistema. Bolesti sistema krvotoka i bolesti sistema za disanje dominiraju u morbiditetu odrasle populacije. Kako u strukturi morbiditeta stanovništva Šumadijskog okruga dominiraju masovne nezarazne bolesti, neophodno je intenziviranje promotivno-preventivnih mera i aktivnosti sa ciljem unapređenja zdravlja stanovništva i rešavanja prioritetnih problema. Preventivne mere i aktivnosti zajedno sa kvalitetnim zdravstvenim uslugama u lečenju oboljenja i stanja, usmerene ka ranom otkrivanju oboljenja i stanja i aktivna promocija zdravlja od suštinskog su značaja za poboljšanje ishoda po zdravlje stanovništva Šumadijskog okruga.

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EXTRAPYRAMIDAL SYNDROMES CAUSED BY ANTIPSYCHOTICS

EKSTRAPIRAMIDALNI SINDROMI IZAZVANI ANTIPSIHOTICIMA

Milana POZNIĆ JEŠIĆ[1], Aleksandar JEŠIĆ[2], Jasmina BABOVIĆ FILIPOVIĆ[1] and Olga ŽIVANOVIĆ[1]

Summary

Introduction. Extrapyramidal syndromes are significant side effects of antipsychotic therapy due to their severity, frequent occurrence and complications. This paper gives a brief summary of the literature with the emphasis on epidemiology, etiology, diagnosis and differential diagnosis, as well as the treatment of extrapyramidal disorders induced by antipsychotics. **Dystonia.** Sustained muscle contractions cause twisting and repetitive movements or abnormal postures. It may appear either as an acute or delayed, i.e. tardive sign. The incidence of dystonia is 2-3% among the patients treated with antipsychotics, and 50% among the ones cured with conventional antipsychotics. **Akathisia.** The main feature of this curious adverse effect is the psychomotor restlessness and the inability to remain motionless. Although akathisia is not very frequent, its incidence and prevalence ranges from 5 to 50% among the treated patients. It is most probably a result of the blockage of dopaminergic receptors. **Parkinsonism.** The most frequent secondary Parkinsonism is the one caused by drugs. The characteristic parkinsonian signs regress 4 to 16 weeks after the discontinuation of antipsychotic therapy. In the era of atypical antipsychotics this adverse effect appears less frequently. **Tardive dyskinesia.** Involuntary choreatic movements may appear days and months after the introduction of continuous use of antipsychotics. The individual susceptibility may play the major role in the development of this side effect. **Conclusion.** Numerous studies have compared conventional and atypical antipsychotics as well as atypical ones with one another in order to decrease the risk of development of extrapyramical side effects as well as to prevent their occurrence and improve their treatment.

Keywords: Basal Ganglia Diseases; Extrapyramidal Tracts; Antipsychotic Agents + adverse effects; Dyskinesias; Dystonia; Psychomotor Agitation; Parkinsonian Disorders

Sažetak

Uvod. Ekstrapiramidalni sindromi predstavljaju značajna neželjena dejstva antipsihotične terapije zbog njihove težine, čestog javljanja i komplikacija. U ovom radu dat je kratak pregled literature sa osvrtom na epidemiologiju, etiologiju, dijagnozu i diferencijalnu dijagnozu, kao i terapiju ekstrapiramidalnih poremećaja indukovanih upotrebom antipsihotika. Brojne studije su se bavile poređenjima konvencionalnih i atipičnih antipsihotika, kao i atipičnih međusobno, u pravcu rizika od javljanja ekstrapiramidalnih sindroma koje nosi njihova upotreba, mogućnostima prevencije i lečenja. **Distonija.** Produžena mišićna kontrakcija koja vodi abnormalnim pokretima ili držanju tela. Može se javiti akutno ili kao odložen neželjeni efekat. Incidencija distonije je 2-3% kod pacijenata lečenih atipičnim antipsihoticima, a kod čak 50% lečenih klasičnim antipsihoticima. **Akatizija.** Glavna karakteristika ovog neželjenog efekta je psihomotorni nemir. Iako ne tako česta, incidenca i prevalencija akatizije varira 5-50% kod pacijenata tretiranih antipsihoticima. Najverovatnije je izazvana blokiranjem dopaminskih receptora. **Parkinsonizam.** Najčešći sekundarni parkinsonizam je parkinsonizam izazvan lekovima. Znaci karakteristični za parkinsonizam se povlače čak 4-16 meseci nakon prestanka uzimanja lekova. U eri atipičnih antipsihotika, ovaj neželjeni efekat se javlja ređe. **Tardivna diskinezija.** Nevoljni pokreti mogu se javiti i mesecima nakon kontinuirane upotrebe antipsihotika. Individualna osetljivost verovatno ima značajnu ulogu u razvoju ovog neželjenog dejstva. **Zaključak.** U brojnim istraživanjima poredili su se klasični i atipični antipsihotici, kao i atipični antipsihotici međusobno, s ciljem da se rizik od pojave ekstrapiramidalnih neželjenih efekata smanji, prevenira njihovo javljanje i poboljša lečenje.

Ključne reči: Bolesti bazalnih ganglija; Ekstrapiramidalni put; Antipsihotici + neželjeni efekti; Diskinezija; Distonija; Akatizija; Parkinsonizam

Introduction

Movement disorders associated with the use of antipsychotic therapy have an important place in clinical practice, and are thus classified as a separate diagnostic category in the classification system of mental disorders (Diagnostic and Statistical Manual of Mental Disorders - DSM IV) (1994) and extrapyramidal syndromes (EPS) are classi-

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Abbreviations:

EPS	− extrapyramidal syndtromes
AP	− antipsyhotic
CAP	− conventional antipsychotics
AAP	− atypical antipsychotics
ADR	− acute dystonic reaction
TD	− tardive dyskinesia

fied as neurological disorders in International Classification of Disorders (ICD 10) (1992).

Antipsychotic (AP) therapy-induced EPS include a variety of iatrogenic-induced movement disorders which can be divided into acute and tardive syndromes. Acute EPS are those that develop within hours or weeks after initiating or increasing doses of AP and they include acute dystonia, akathisia and Parkinsonism. Tardive dyskinesia and tardive dystonia are delayed-onset syndromes and usually develop after a prolonged use of AP.

Neuroleptic malignant syndrome is an idiosyncratic, potentially life-threatening and often diagnostically unrecognized condition induced by AP, which manifests with sudden fever, autonomic nervous system instability, EPS and altered state of consciousness. It is often accompanied by elevated serum creatine kinase levels, impaired liver and renal function, leukocytosis, disturbed electrolyte balance and coagulation, as well as ECG changes [1]. Due to its uniqueness in terms of complexity of the clinical picture, diagnosis and therapeutic approach, neuroleptic malignant syndrome will not be covered by this text [2-4].

The term ”neuroleptic”, meaning ”to fix or hold a neuron,” was used to describe the neurological adverse effect of conventional antipsychotics (CAP) rather than their therapeutic effects. In earlier clinical practice, the procedure for treating the patients with psychotic disorders was increasing the dose of CAP to the so-called ”neuroleptic threshold,” i.e. the dose when EPS occurs, and waiting for the therapeutic response. The attitudes have changed due to the appearance of atypical antipsychotics (AAP): clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. The main characteristic of AAP is a reduced risk of both acute and tardive EPS [5,6]. It is also one of their main characteristics and advantages associated with better treatment acceptance and compliance. Some of them, such as clozapine, have proved to be effective for the treatment of resistant patients, and less commonly cause increased serum concentrations of prolactin [7].

It is believed that antagonism of dopamine D2 receptors is involved not only in antipsychotic effects, but also in causing EPS. Studies in which positron emission tomography (PET) was used have shown that antagonism of 60-70% of dopamine D2 receptors is required for CAP to be effective, and 75-80% of D2 receptor blockade leads to the occurrence of acute EPS [8,9]. Most authors estimate that EPS appear in about 90% of patients treated with CAP, such as haloperidol, in which the therapeutic range is the narrowest and therapeutic activity and EPS mutually inseparable [6,10]. The use of second generation antipsychotics, in particular clozapine, is associated with a lower risk of movement disorders, compared to the use of CAP [11,12]. Goldstein [13] points out that long-standing use of clozapine was not associated with increased occurrence of tardive dyskinesia, dystonia, akathisia and Parkinsonism.

The mechanism of ”atypicality” of new-generation antipsychotics is still being discussed. Some authors believe that this is a consequence of pharmacodynamic characteristics of AAP, such as increased antiserotonergic, anticholinergic activity, along with antidopaminergic one [14]. Others argue that the difference is primarily in the pharmacodynamics, due to not so strong and transient binding to D2 receptors which are atypical when compared to conventional AP [15]. D2 receptors are least occupied dose-independently by clozapine and quetiapine at therapeutic values, which are, therefore, associated with the lowest risk of EPS [9,16,17]. Kane [6] states that quetiapine is a new-generation antipsychotic with the most desirable profile of adverse neurological effects since the incidence of EPS is reduced to the level of placebo, even at high therapeutic doses. Unlike clozapine and quetiapine, risperidone and olanzapine show a greater tendency to striatal D2 receptors, leading to the more frequent occurrence of EPS. Although they have a higher affinity for 5-HT2A receptors, at higher doses they induce the occurrence of EPS more frequently. There are few comparable data available for assessing the risks carried by AAP for the induction of EPS, but, the order is as follows according to Tarsy [14]: clozapine <quetiapine<olanzapine. At doses higher than 8mg/day risperidone carries a greater risk compared to olanzapine. The superiority of AAP comes mainly from the comparisons with inappropriately high doses of CAP, primarily haloperidol. In clinical practice, AAP doses are increasingly elevated, with the exception of risperidone; thus the possibility to balance the risks of EPS in future is greater.

In spite of being significantly reduced, the risk of inducing EPS associated with the use of AAP does exist; hence the need for further research directed towards the treatment of choice has arisen.

Metabolic syndrome, also called ”EPS of the new millennium” is an extremely significant side effect of AAP [18]. There is no doubt that the risk of weight gain, impaired glucose tolerance, hyperlipoproteinemia, hypertension, increased risk of diabetes and cardiovascular disorders affects the choice of an antipsychotic drug that is to be introduced into therapy.

Dystonia

Dystonia is a short or prolonged muscle contraction which leads to abnormal movement or posture. Unlike an acute dystonic reaction (ADR), in which a muscle contraction is transient, in tardive dystonia it is persistent and usually occurs after years of use of antipsychotics, but may also occur after a significant-

ly shorter exposure to AP therapy. Antipsychotic-induced dystonia is typically focal, although in rare cases it can affect several muscle groups. It manifests in the cranial, pharyngeal, cervical and axial muscles leading to oculogyric crisis, stiff jaw, tongue protrusion, torticollis, retrocollis, laryngeal, pharyngeal spasm, dysarthria, dysphagia, and sometimes difficulties in breathing, cyanosis, opisthotonus. Limb muscles are less commonly affected; hence tardive dystonia is sub-classified as dyskinesia by some authors [19]. Dystonia is a very unpleasant experience for patients, sometimes even painful.

Of all patients treated with neuroleptics, about 2-3% will develop ADR in the first few days after starting the drug [20]. If a highly potent classical AP is used, that percentage can increase up to 50% [20]. Half of the ADR reported cases is described in the first 2 days of exposure to AP, and 90% in the first 4 days [21]. Daily rhythm with a significantly higher incidence in the second half of the day was also observed [20].

Risk factors include primarily the duration of use and high dose of AP, younger age, male gender, mental retardation, positive family history of dystonia, previous dystonic reaction, a recent cocaine and alcohol abuse [21]. Dystonia can sometimes be caused by antiemetics and some antidepressants. All antipsychotic drugs, including AAP, may lead to dystonia, although it seems that they are less common with the use of antipsychotic drugs having a more pronounced anticholinergic action. The duration of dystonia may be prolonged when depot preparations of antipsychotics are used.

The pathogenesis is still unclear, although it is associated with secondary hypersensitivity of blocked D2 receptors.

When diagnosing neuroleptic therapy-induced dystonia, it is important to exclude neurological disorders that can also be the cause. An inexperienced doctor can often misinterpret this phenomenon as histrionic behavior.

Tardive dystonia varies differentially diagnostically from tardive dyskinesia not only because of its phenomenology, but also because it is more common in younger people in whom it may be alleviated by the use of anticholinergics, unlike tardive dyskinesia which may even be aggravated [22].

Despite the unclear pathophysiology, treatment with ADR is very successful. Intravenous use of anticholinergics is effective and fast acting and the result is sometimes achieved within minutes. The recommended initial dose of biperiden is 2 mg parenterally and 2mg per os, with a dose of 2mg/day per os in the next 1-2 weeks. The preventive use of anticholinergics is justified in patients at higher risk (younger men and those with previous ADR experience) [20]. If ADR is not treated, it can last for hours or days. When antipsychotic therapy is required, atypical group is indicated, such as aripriprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone, which showed a lower risk of inducing EPS, particularly acute dystonia and Parkinsonism. In case of tardive dystonia, a change of antipsychotic is indicated – the introduction of clozapine is recommended, and sometimes the application of high doses of anticholinergics, such as trihexyphenidyl, may be effective [23]. Blockade of motor neurotransmission with Botulinum toxin in the affected muscles is successful in patients, but the improvement is usually only temporary [24]. There is a possibility of spontaneous remission, but in most cases, dystonia persists for years and is extremely debilitating and stigmatizing. Data from the literature point to the effectiveness of other medicament and non-medicament procedures in the treatment of tardive dystonia, such as tetrabenazine, reserpine, procyclidine, benztropine, baclofen, deep brain stimulation, levodopa and physiotherapy.

Akathisia

The term akathisia was first mentioned by Haškovec in 1903 and the question whether it is a movement disorder, mental disorder or both arose at the beginning of the twentieth century [25].

Akathisia is a frequent and serious adverse effect of treatment with antipsychotic drugs. It includes half of EPS [21] and is considered one of the most common movement disorders induced by blocking dopamine receptors with neuroleptics and antiemetics [20]. Akathisia may also be caused by serotonergic agents, serotonin reuptake inhibitors and cocaine.

This syndrome consists of a subjective and objective component. The patients suffer from the feeling of restlessness and an irresistible urge to move. They describe a very upsetting experience of pressure, nervousness and tension. Objectively, an increased motor activity consisting of complex, often meaningless stereotyped and repetitive movements is recorded. Motor restlessness is typically expressed as full body movements, but sometimes only as ”restless legs” in the form of myoclonus of the feet. The patients cross and uncross their legs, fidget in a chair or bed, hop, stand up and soon return to the previous position, walk as if marching on the spot.

According to the time of onset in relation to the initiation or increase of AP therapy and duration of symptoms, akathisia can be divided into acute, tardive, chronic and withdrawal akathisia following the discontinuation of AP. Acute akathisia occurs shortly after the initiation or increased dose of AP within two weeks, and tardive akathisia develops after at least three months of therapy, regardless of the change in an antipsychotic drug or its dose. Acute and tardive akathisia as well as akathisia following the discontinuation of AP can persist for more than 3 months, which leads to chronic akathisia [26]. The aforementioned forms of akathisia do not differ significantly from acute akathisia in objective motor symptoms, whereas the subjective component may be less pronounced over time.

Data on the incidence and prevalence are inconsistent due to different diagnostic approaches [26]. The prevalence of akathisia varies widely from 5 to 36.8%. Acute akathisia occurs in 25% of patients

treated with an antipsychotic [21]. Data from CATIE show that akathisia occurs in 10 to 20% of patients treated with atypical AP, which is less than 20 to 52% when typical neuroleptics are used [21]. No significant evidence of age and gender such as a predisposition has been found [21,26]. There is a correlation between the neuroleptic potency for D2 receptors and doses in relation to how pronounced symptoms of akathisia are [20].

Pathophysiological mechanism of akathisia is still unclear [26].

Some authors believe that the diagnosis of akathisia can be made solely on the basis of movement disorders, while others point out their existence as a mechanism by means of which the patients struggle and reduce the feeling of restlessness and urge to move. However, the proper diagnosis of this problem according to the current criteria requires both objective and subjective component. In the case of the motor component alone, some authors regard pseudoakathisia as tardive dyskinesia of the lower extremities [26]. Others classify pseudoakathisia into a subcategory of true akathisia with less pronounced symptoms, the objective component being dominant [26]. Doctors sometimes misinterpret this condition as psychotic agitation, and thus promptly introduce an antipsychotic and thereby worsen or prolong this condition. Since the subjective component of akathisia may lead a patient to suicide, this situation must not be ignored or remain unrecognized.

Akathisia may persist for the duration of antipsychotic therapy, and usually ceases after the discontinuation of AP. Therefore, when treating akathisia, the dose of AP should preferably be reduced first or an atypical drug should be chosen. Clozapine and quetiapine proved to carry the lowest risk in causing akathisia [21]. The symptoms of akathisia can also be reduced by nonselective liposoluble β-blockers (propranolol initially 30mg/day in three doses, with gradual increase to 120mg/day, if necessary) [26]. Benzodiazepines (lorazepam 1.5-3mg/day and clonazepam 0.5mg/day) are also indicated, especially in the case of persistent subjective symptoms [26]. Clonazepam may be preferable to diazepam due to its long half-life. Effectiveness of anticholinergics has not been confirmed [26]. Clonidine has shown a positive effect, but its use is associated with serious side effects such as sedation and orthostatic hypotension [26]. Research on the effectiveness of amantadine, ritanserin and piracetam is currently underway.

Antipsychotic-induced Parkinsonism

Drug-induced Parkinsonism is the second most common form of Parkinsonism in elderly people after idiopathic Parkinson's disease. The interval between the application of the drug and the onset of Parkinsonism is variable and ranges from a few days to several months.

Unlike Parkinson's disease, the symptoms are often bilateral and symmetrical. There is a triad of bradykinesia, muscle rigidity and tremor, although it is usually less pronounced. Other symptoms and signs include unsteady gait, festination, reduced synkinesis, anteropulsion, hypomimia, sialorrhea and seborrhea. Postural tremor is more common than resting tremor. Tremor of the lips and perioral muscles can be observed as well, which is also called "rabbit syndrome".

In patients who have used AP, the prevalence is about 15%, although it is difficult to determine with precision due to the fact that epidemiological studies usually classify it as a form of Parkinsonism or generally drug-induced movement disorder [27].

Risk factors include: age, female gender, type of drug used, dose and duration of therapy, cognitive deficit, acquired immunodeficiency syndrome, tardive dyskinesia and early-onset extrapyramidal disorder [27].

Pathophysiological mechanism is associated with dopaminergic D2 and serotonergic 5-HT2A receptors blockade and low affinity of particular AP to acetylcholine receptors.

Although drug-induced Parkinsonism is considered a reversible condition, in most cases it usually lasts up to 4 months, it can last 6-18 months, and in 15% of cases it has been even described as persistent [27]. In case of persistent symptoms, antipsychotic-induced Parkinson's disease should be taken into consideration, and it should be treated with dopaminergics. Symmetrical postural tremor associated with drug-induced Parkinson's disease can be mistaken for essential tremor in the elderly which is mono-symptomatic. Information on taking AP, coexistence of orofacial dyskinesia, limb muscles dyskinesia and akathisia may be helpful for the proper diagnosis. Since there is no nigrostriatal degeneration as with Parkinson's disease, Dopamine Transport SPECT Imaging (DaTscan) does not record a reduced dopamine reuptake in case of drug induced-Parkinsonism. When the differential diagnosis is being made in relation to vascular Parkinsonism, which is usually also symmetrical, the history of previous vascular incident, as well as risk factors for cerebrovascular diseases should be taken into consideration.

Bearing in mind that the quality of life of patients with symptoms of drug induced-Parkinsonism declines drastically, and that its course is usually reversible, it is of high importance to recognize this condition early and employ appropriate therapeutic measures. The first step in treating patients is to reduce the dose of antipsychotic drugs (if possible) or substitute the applied AP with another, usually atypical one. The treatment of choice does not really exist, although the use of anticholinergics is a part of everyday practice often with favorable results [27]. They should be avoided in the elderly because of adverse effects such as deterioration in cognitive function, urinary infection, closed-angle glaucoma precipitation. Acetylcholinesterase inhibitors may serve as an alternative. Amantadine has proved successful so far only in small studies, although it is not well-tolerated by elderly patients [27]. The use of dopaminergic drugs is

not justified in this type of Parkinsonism. Clozapine and quetiapine have a significant advantage in the treatment of psychotic symptoms in Parkinson's disease compared to other atypical and typical antipsychotics [27]. In case of the discontinuation of AP, the symptoms may last from 2 weeks up to 3 months in elderly patients. In them anticholinergic therapy can be continued until these symptoms have completely disappeared [28].

Tardive dyskinesia

It is manifested by involuntary choreoathetoid movements of the orofacial region, extremities, trunk and respiratory muscles. The movements are more pronounced with excitement, and disappear during sleep. Sometimes the patients set up their mind to decrease the intensity of the involuntary movements and succeed in doing so, but for a short time. It should be noted that a significant number of patients do not notice these involuntary movements or are not bothered by them [29]. It is family who is usually upset more than the patients themselves.

Tardive dyskinesia (TD) can occur in all patients treated with AP [12]. It develops after months or years of continuous use of antipsychotics. The condition can also persist after the discontinuation of AP or may even be irreversible.

The incidence of TD associated with CAP therapy in long-term studies is 5% per year in adults [14] and cumulative annually 25-30% in the elderly [17]. With atypical AP treatment, the incidence is significantly lower [12]. When risperidone and olanzapine are used [21], the incidence becomes the same as the incidence of spontaneous TD in patients with schizophrenia. Some extremely rare cases were described resulting from the use of clozapine [30].

The incidence of TD varies depending on the type and dose of AP, duration of use, gender, patient's age, although there is a belief that most patients will develop TD if treated long enough. Elderly patients as well as female patients are at a greater risk [29]. Risk factors also include brain damage, dementia, mood disorders, duration of AP therapy, use of anticholinergic antiparkinsonian therapy, previous occurrence of EPS.

The early occurrence of EPS, being non-Caucasian in race, older age, genetic predisposition to develop schizophrenia and the occurrence of TD as a side effect of AP are mentioned as the leading risk factors for the occurrence of TD in schizophrenic patients [31]. The correlation between early EPS and TD may be an indicator of individual variations in susceptibility of dopamine system, and therefore a possible early form of prevention of TD by the right choice of AP.

Kane [6] found the greater tendency of patients suffering from mood disorders to develop tardive dyskinesias than those with schizophrenia. Bleuler [32] and Kraepelin [33] noted as early as the pre-antipsychotic era that tardive dyskinesia could occur spontaneously in patients with psychosis. These observations have been confirmed by modern research [14]. Tenback [31] mentions the occurrence of spontaneous TD more commonly in schizophrenic patients not treated with AP as well as in their first degree relatives, and states that TD may be associated with genetic vulnerability for the occurrence of schizophrenia.

Spontaneous TD occurs in about 0.5% per year of age in the general "non-psychiatric" population after the age of 60 [21]. There is also higher, but very variable prevalence of orofacial dyskinesias in the elderly demented people, with or without psychotic disorders or mood disorders.

There are data from small studies on genetic vulnerability as a risk factor and the dopamine D2 receptor gene DRD2 as a predisposition for the development of TD in patients with schizophrenia [34].

TD is associated with increased mortality and higher incidence of respiratory infections.

Pathophysiologically most convincing evidence suggests that TD is a result of primarily neuroleptics-induced dose-dependent super-sensitivity of D2 receptors in the nigrostriatal pathway.

Should TD occur, it would be indicated to disconinue AP. However, many patients require the continuation of this therapy. In that case the dose of CAP should be reduced to the minimum effective dose and/or replaced with an antipsychotic whose administration carries the lowest risk of TD, such as clozapine [23] or quetiapine [6]. The use of vitamin E, valproates, essential fatty acids and benzodiazepines has also been considered, but the evidence is inconclusive for any of the above options [29].

Conclusion

Extrapyramidal syndromes are frequent, severe, debilitating and stigmatizing consequences of neuroleptic therapy. In recent years conventional antipsychotics have been replaced by the atypical ones in the therapeutic approach primarily due to reduced risk of causing both acute and tardive extrapyramidal syndroma. Since atypical antipsychotics represent a new generation, longer studies regarding the mentioned risks are necessary, especially when it comes to tardive movement disorders. In spite of having many benefits, the adverse effects of atypical antipsychotic drugs are far from negligible. Metabolic syndrome, also known as "extrapyramidal syndrome of the new millennium", can be more important compared to the involuntary movement disorders in terms of morbidity, disability and mortality. Treatment of certain iatrogenically induced extrapyramidal syndroma with anticholinergics, beta blockers, anxiolytics and other aforementioned drugs and methods has shown good, but not always completely successful results. Therefore, further research is required with the hope to improve prevention and diagnosis, reduce or eliminate unwanted symptoms already manifested and the recurrence of extrapyramidal syndroma in the patients with previous experience of this stigmatizing and very important side effect in the treatment of primary disorder.

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PRIKAZI SLUČAJEVA
CASE REPORTS

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MUCINOZNI CISTADENOFIBROM JAJNIKA

MUCINOUS CYSTADENOFIOBROMA OF THE OVARY

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Sažetak

Uvod. Cistadenofibromi jajnika su tumori porekla površnog celomskog epitela kod kojih je karakteristično postojanje znatne stromalne komponente izgrađene od vezivnog tkiva sa inkorporiranom jednom ili više cista. Mucinozni benigni cistadenofibromi su veoma retke forme ovih tumora. **Prikaz slučaja.** U radu je prikazan slučaj pacijentkinje stare 62 godine, kojoj je odstranjen desni jajnik sa jajovodom. Patohistološkom analizom utvrđeno je postojanje multilokularne cistične formacije obložene jednoslojnim mukoproduktivnim epitelom endocervikalnog tipa. Unutar multilokularne formacije nađeno je solidnije polje sa izraženom stromalnom komponentom od gustog, delom hijalinizovanog vezivnog tkiva. Promena je dijagnostikovana kao mucinozni cistadenofibrom. Za razliku od seroznih tumora jajnika, u mucinoznim oblicima tumorsko tkivo retko ima formu cistadenofibroma ili adenofibroma. S obzirom na retko pojavljivanje, prikazali smo slučaj cistadenofibroma kod žene u sedmoj deceniji života. **Zaključak.** Cistadenofibromi i adenofibromi su diferencijalno-dijagnostički vrlo slični raznim malignim tumorima te je izuzetno važna pravilna dijagnostika ovih tumora.

Ključne reči: Cistadenom; Fibrom; Jajnik; Ovarijalna cista; Žensko; Srednje godine; Diferencijalna dijagnoza

Summary

Introduction. Cystadenofibromas are tumors of the ovary which originate from the surface coelomic epithelium. Benign mucinous cystadenofibroma is a very rare form of these tumors, which consists of dominant stromal component of the connective tissue and one or more cysts. **Case report.** The case of a 62-year-old female with tumor of right ovary is reported in this paper. Histologically, tumor of the ovary had multilocular cystic formation, lined by a single-layer of mucoproductive cylindrical epithelium – endocervical type. In one area of tumor, the stromal component was abundant and made from partially hyalinised dense connective tissue. Mucinous cystadenofibroma was diagnosed on the basis of histological examination. Since the mucinous type of cystadenofibroma or adenofibroma is rare, this case has been chosen to be presented. **Conclusion.** Mucinous cystadenofibromas are differentially-diagnostically very similar to different malignant tumors and it is extremely important to make correct diagnosis of these neoplasms.

Key words: Cystadenoma; Fibroma; Ovary; Ovarian Cysts; Female; Middle Aged; Diagnosis, Differential

Uvod

Tumori ovarijuma odlikuju se velikom raznovrsnošću. Histološka klasifikacija ovarijalnih tumora, prema Svetskoj zdravstvenoj organizaciji, izvedena je iz histogeneze ovarijuma, te se klasifikuju kao tumori porekla površnog celomskog epitela, tumori germinativnog epitela, tumori gonadalne strome i polnih traka [1,2]. Tumori porekla celomskog epitela su najzastupljeniji i čine 58% svih tumora jajnika [3]. U odnosu na histološke odlike ćelija, tumori porekla celomskog epitela mogu se podeliti na serozne, mucinozne, endometrioidne, svetloćelijske, Brenerov tumor i tumore mešovitog tipa [3,4].

Histološke podvarijante ovih tumora su u vidu ciste, adenofibroma ili cistadenofibroma. Cistadenofibromska i adenofibromska varijanta izuzetno su retke i često nisu pojedinačno opisane u literaturi [5,6].

Mucinozni cistadenofibrom je benigni tumor koji se odlikuje prisustvom čvrstih fibroznih polja

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sa „uronjenim" manjim adenoidnim ili cističnim formacijama koje su obložene cilindričnim mukoproduktivnim epitelom. Mucinozni tumori su obloženi ili visokim cilindričnim epitelom endocervikalnog tipa ili intestinalnim epitelom sa peharastim ćelijama [7–10].

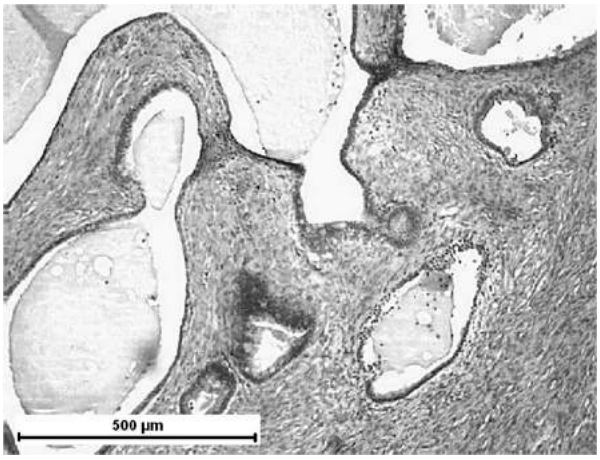
Prikaz slučaja

Pacijentkinji staroj 62 godine hirurški su odstranjeni cistična formacija desnog jajnika i desni jajovod i poslati su na patohistološki pregled. Makroskopskim pregledom opisani su jajovod dužine 5 cm i kuglasta, multilokularna cista dimenzija 5 x 3 cm. Površine obe strukture su glatke i sivkaste. Na poprečnim presecima tkivo jajnika je zamenjeno multilokularnom cistom. Zid ciste je tanak i gladak. Unutar ciste, uočeno je sivobeličasto polje dimenzija 2 x 1 cm, čvršće konzistencije sa brojnim malim šupljinama koje ispunjava sluz.

Nakon rutinske histološke obrade materijala: fiksacije u 10% formalinu, dehidratacije, kalupljenja u parafinu, sečenja na debljinu od 4 μm i bojenja hematoksilin-eozin metodom, izvršena je histološka analiza. Histološkom analizom uzoraka uočeno je da je tkivo jajnika najvećim delom zamenjeno multilokularnom cistom. Ciste su obložene pravilnim jednoslojnim mukoproduktivnim epitelom endocervikalnog tipa bez polimorfije i mitoza. Makroskopski opisano je solidno polje, histološki, odgovara delu tumora sa izraženom stromalnom komponentom koja je sagrađena od gustog, delom hijalinizovanog vezivnog tkiva. U stromalnoj komponenti se nalaze adenoidne formacije obložene mucinoznim endocervikalnim cilindričnim epitelom **(Slika 1)**. Isečci iz jajovoda su bili odgovarajućih histoloških karakteristika. Opisane histološke strukture u jajniku su dijagnostikovane kao mucinozni cistadenofibrom ovarijuma.

Diskusija

Cistadenofibrom može biti svetlećelijskog, endometrioidnog i mucinoznog tipa. Mucinozni tip cistadenofibroma je najređi [10]. Koliko je zaista retko oboljenje vidi se po studiji Kao i Norrisa, gde je analizirano 16 slučajeva cistadenofibroma ovarijuma sa neuobičajenim vrstama epitela [11]. U pomenutoj studiji, u dvanaest slučajeva bili su primeri endometrioidnog tipa, tri su bila svetlećelijska, a samo jedan slučaj mucinoznog cistadenofibroma. Slična je i studija koju su sproveli Yaker i Benirschke (1975), gde je u periodu od 9 godina ispitivana učestalost pojedinih



Slika 1. *Mikrofotografija mucinoznog cistadenofibroma jajnika (HE, 10x)*
Fig. 1. *Microphotography of mucinous cystadenofibroma ovarii (HE, 10x)*

histoloških tipova ovarijalnih tumora [12]. Od ukupnog broja, 5,4% (11/204) bili su serozni cistadenofibromi, dok slučaj mucinoznog cistadenofibroma nije registrovan.

Najčešće se javljaju benigni ovarijalni cistadenofibromi u četvrtoj i petoj deceniji, dok pojedini izvori iz literature navode da se svetlećelijski i mucinozni tip javljaju jednu do dve decenije kasnije [10,12]. S obzirom da je pacijentkinja u našem slučaju stara 62 godine, starosno doba pacijentkinje odgovara navodima u literaturi.

Benigni mucinozni cistadenofibrom može se javiti udruženo sa malignim neoplazmama jajnika kao što su primarni mucinozni cistadenokarcinom jajnika [13,14], ili sinhrono sa metastatskim mucinoznim cistadenokarcinomom primarne lokalizacije u apendiksu, želucu, crevima, pankreasu, žučnoj kesi, grliću materice ili na urahusu [15], što naglašava značaj pravilne i precizne dijagnostike ove neoplazme.

Zaključak

Benigni mucinozni cistadenofibrom izuzetno je retka neoplazma jajnika, međutim to ne umanjuje značaj dijagnostike ove neoplazme, posebno zato što je zabeleženo da može evoluirati u malignu formu tumora – mucinozni cistadenofibrokarcinom, kao i zbog udruženog javljanja sa primarnim i metastatskim malignim neoplazmama jajnika.

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OBAVEŠTENJE O POVLAČENJU RADA
RETRACTION NOTE

Na inicijativu uredništva Medicinskog pregleda i uz saglasnost autora, članak autora Gajović O, Todorović Z, Nešić Lj, Lazić Z. "Lymska bolest – diferencijalne teškoće u intepretaciji seroloških rezultata" koji je objavljen 2010 godine (volumen 63, broj 11-12, str. 839-843), povlači se jer se radi o plagijatu rada autora Đaković Rode O, Ružić Sabljić E. "Lyme borelioza – diferencijalno dijagnostičke poteškoće u interpretaciji seroloških rezultata" objavljenog u časopisu Infektološki glasnik 2002. godine (volumen 22, broj 2, str. 45-49).

IN MEMORIAM
IN MEMORIAM

Prof. dr MILIVOJ DEDIĆ
(1924 - 2012)

Profesor, radiolog, stručnjak, kolega, rukovodilac, vizionar, otac, suprug, deda, strasni ljubitelj konjičkog sporta − sve to bio je naš Milivoj Dedić.

Rođen je 1924. godine u Somboru, gde je završio i gimnaziju, a celog svog života ostao je odan ravnici i Vojvodini. Još od malena, kad je bio deran, kako je često nazivao mlađe kolege, zavoleo je konje. Puno je čitao iz različitih knjiga, ozbiljno izučavao pojedine osobine ovih plemenitih životinja i izgradio sopstveni odličan osećaj da izabere mlade konje koje je potom pažljivo trenirao i uzgajao. Uspevao je da od njih napravi pobednička grla, koja su uvek bila visoko plasirana na takmičenjima širom Jugoslavije, ali i na internacionalnim prostorima. Kinderi, Lančester, Best, Alonso imena su samo nekih od njegovih ljubimaca o kojima je s ponosom pričao. Bio je dugogodišnji predsednik konjičkog kluba *Vojvođanin* u Somboru i izborio se da, prvi put u istoriji, Sombor bude domaćin velikog jugoslovenskog kasačkog derbija.

Kao što je imao oko i osećaj da prepozna buduća pobednička grla, tako je i u medicini, opredelivši se za radiologiju i počevši specijalizaciju u Beogradu davne 1951., uspevao da pre svih shvati vrednost tehnološkog napretka i uvođenja savremenih aparata u kliničku praksu.

Kao stipendista fondacije Kiri, 1959. godine, Dedić je bio na stručnom usavršavanju na radiološkim institutima u Parizu, kao gost Francuskog radiološkog društva. Po povratku je prvi uradio mamografiju u tadašnjoj Jugoslaviji. Objavio je 1962. godine i prvi stručni rad o mamografiji u zemlji. Iste te godine na Drugoj hirurškoj klinici Medicinskog fakulteta u Beogradu, njegovim angažovanjem nabavljen je 12-ventilni rtg aparat sa TV lancem, koji je zajedno sa istim takvim u Ajndhofenu, bio prvi takve vrste u Evropi, o čemu svedoči i francuski dugometražni dokumentarni film *Kroz nauku i tehniku naše epohe*.

Godine 1963. profesor Dedić je došao u Novi Sad, gde je u Kiničkoj bolnici postavljen za šefa dijagnostičkog odeljenja. Od tada, razvoj radiologije u tadašnjoj bolnici u Novom Sadu, danas Kliničkom centru Vojvodine, potpuno je prožet njegovim svakodnevnim radom i doprinosom. Već sledeće 1964. godine nastaje Zavod za radiologiju pod njegovim vođstvom, sa dva odeljenja za radioterapiju i radiološku dijagnostiku. Njegova ogromna energija, upornost i snaga, ravna snazi kasa najrasnijeg konjičkog grla, nije priznavala prepreke. Zavod se širi i prostorno i tehnički oprema − 1965. montira se rtg aparat sa TV lancem i aparatura za angiodijagnostiku i nabavljaju se u to vreme najsavremeniji aparati za radioterapiju. Od tada pa nadalje, Institut za radiologiju razvija se rame uz rame sa svim evropskim centrima i, Dedićevim ličnim angažovanjem, uvode se sve tad postojeće kontrastne invazivne metode kao što su limfografija, splenoportografija i druge. Vrlo brzo započinje i razvoj interventne radiologije. Zavod prerasta u Institut 1970. godine, a kasnije 1976. integracijom sa 5 drugih instituta i centralnom apotekom ulazi u sastav Instituta zajedničkih medicinskih službi, a na mesto direktora postavljen je prof. Dr Milivoj Dedić.

U Institutu za radiologiju 1979. i 1980. godine nabavljaju se ultrazvučni i prvi aparat za kompjuterizovanu tomografiju − CT skener. Svi mi koji iole pokušavamo da rukovodimo i kuće u kojima radimo postavimo na neke više standarde, znamo

koliko je teško pronaći finansijska sredstva i ubediti zajednicu u neophodnost nabavke nove aparature. Tako je bilo uvek, i mogu samo da zamislim koliko razmišljanja, taktike i energičnih poteza je bilo potrebno prof. Dediću da u to vreme obrazloži neophodnost kupovine nečega, čiju vrednost i funkciju još niko u okolini nije video. Za razvoj struke prof. Dedić je dobio 1980. godine Oktobarsku nagradu Grada Novog Sada.

Svoj radni vek u Institutu za radiologiju završio je 1989. godine kad je otišao u penziju, ali radiologiju nije napustio do poslednjeg dana. U Somboru je nastavio privatnu praksu i sve do svog poslednjeg kobnog junskog dana radio je bez prekida u kontinuitetu 20 godina, bez korišćenja godišnjeg odmora, jer je za njega radiologija bila i rad i odmor. Sve zajedno, ako se uzmu u obzir i dve poslednje godine studija kada je bio demonstrator na predmetu, radiologijom se ukupno bavio 63 godine − više od 6 decenija. Postojano i uporno radio je za svoju porodicu, odan tradicionalnim vrednostima, a pored supruge Verice i jedinca Srđana koji je nastavio medicinsku tradiciju, poseban podstrek i izvor energije bili su mu unuci Kristina i Stefan koje je neizmerno voleo i na koje je bio ponosan.

Od momenta kad sam stupila na mesto upravnika radiologije, u svim situacijama gde je trebalo neke stvari preseći, izboriti se sa predrasudama i lošim namerama, pratio me je komentar: „E, prof Dedić bi sad ovako ili sad onako". Ti komentari nisu poticali samo od kolega, nego i tehničara, službenica, svih koji su ga poznavali. I ako nekad nisam verovala u sve što čujem, i činilo mi se da neke stvari već prerastaju u mit, danas ne mogu a da ne zastanem sa izuzetnim poštovanjem prema čoveku koji je ostavio takav trag u vremenu i prostoru za sobom i ostaje mi samo da se nadam da će vojvođanska radiologija nastaviti da ide tako silovito i odlučno napred kako je kroz vreme koračao prof. Milivoj Dedić.

Slava mu.

Prof. dr Sanja Stojanović
Upravnik Centra za radiologiju KCV

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– Koristiti mere metričkog sistema prema Internacionalnom sistemu mera (*International System Units – SI*). Temperaturu izražavati u Celzijusovim stepenima (°C), a pritisak u milimetrima živinog stuba (mmHg).

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Uvod sadrži precizno definisan problem kojim se bavi studija (njegova priroda i značaj), uz navođenje relevantne literature i sa jasno definisanim ciljem istraživanja i hipotezom.

Materijal i metode treba da sadrže podatke o načinu dizajniranja studije (prospektivna/retrospektivna, kriterijumi za uključivanje i isključivanje, trajanje, demografski podaci, dužina praćenja). Statističke metode koje se koriste treba da budu jasne i detaljno opisane.

Rezultati predstavljaju detaljan prikaz podataka dobijenih tokom studije. Sve tabele, grafikoni, sheme i slike moraju da budu citirani u tekstu, a njihova numeracija treba da odgovara redosledu pominjanja u tekstu.

Diskusija treba da bude koncizna i jasna, sa interpretacijom osnovnih nalaza studije u poređenju sa rezultatima relevantnih studija publikovanim u svetskoj i *domaćoj* literaturi. Navesti da li je hipoteza istraživanja potvrđena ili opovrgnuta. Izneti prednosti i ograničenja studije.

Zaključak u kratkim crtama mora da odbaci ili potvrdi pogled na problem koji je naveden u Uvodu. Zaključci treba da proizilaze samo iz vlastitih rezultata i da ih čvrsto podržavaju. Uzdržati se uopštenih i nepotrebnih zaključivanja. Zaključci u tekstu moraju suštinski odgovarati onima u Sažetku.

5. Literatura. Literatura se u tekstu označava arapskim brojevima u uglastim zagradama, prema redosledu pojavljivanja. Izbegavati veliki broj citata u tekstu. Za naslove koristiti skraćenice prema *Index Medicus*-u (http://www.nlm.nih.gov/tsd/serials/lji.html). U popisu citirane literature koristiti Vankuverska pravila koja precizno određuju redosled podataka i znake interpunkcije kojima se oni odvajaju, kako je u nastavku dato pojedinim primerima. Navode se svi autori, a ukoliko ih je preko šest, navesti prvih šest i dodati et al.

Članci u časopisima:

∗ *Standardni članak*

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.

∗ *Nisu navedena imena 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(ci) kao autor*

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.

∗ *Rad u zborniku radova*

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.

∗ *Disertacije i teze*

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

Elektronski materijal

∗ *Članak u Časopisu u elektronskoj formi*

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

∗ *Monografije u elektronskoj formi*

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.

∗ *Kompjuterski dokument (file)*

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

6. Prilozi (tabele, grafikoni, sheme i fotografije).

Dozvoljeno je najviše šest priloga!

– Tabele, grafikoni, sheme i fotografije dostavljaju se kao posebni dokumenti, na posebnim stranicama.

– Tabele i grafikone pripremiti u formatu koji je kompatibilan sa programom *Microsoft Word for Windows.*

– Slike pripremiti u JPG, GIF TIFF, EPS i sl. formatu

– Svaki prilog numerisati arapskim brojevima, prema redosledu njihovog pojavljivanja u tekstu.

– Naslov, tekst u tabelama, grafikonima, shemama i legendama navesti na srpskom i na engleskom jeziku.

– Objasniti sve nestandardne skraćenice u fusnotama koristeći sledeće simbole: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendama mikrofotografija navesti korišćenu vrstu bojenja i uvećanje na mikroskopu. Mikrofotografije treba da sadrže merne skale.

– Ukoliko se koriste tabele, grafikoni, sheme ili fotografije koji su ranije već objavljeni, u naslovu navesti izvor i poslati potpisanu izjavu autora o saglasnosti za objavljivanje.

– Svi prilozi biće štampani u crno-beloj tehnici. Ukoliko autori žele štampanje u boji potrebno je da snose troškove štampe.

7. Dodatne obaveze

Ukoliko autor i svi koautori nisu uplatili članarinu za Medicinski pregled, rad neće biti štampan. Radovi koji nisu napisani u skladu sa pravilima Medicinskog pregleda, neće biti razmatrani. Recenzija će biti obavljena najkasnije u roku od 6 nedelja od prijema rada. Uredništvo zadržava pravo da i pored pozitivne recenzije donese odluku o štampanju rada u skladu sa politikom Medicinskog pregleda. Za sva dodatna obaveštenja obratiti se tehničkom sekretaru:

Društvo lekara Vojvodine
Vase Stajića 9
21000 Novi Sad
Tel. 021/521 096; 063/81 33 875
E-mail: dlv@neobee.net

INFORMATION FOR AUTHORS

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This journal 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 auto-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 practise.

6. Case reports – up to 6 pages – deal with rare casuistry from practise 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 in 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.

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

– in electronic format to the address **dlv@neobee.net**

– the 2 printed copy to the address

Drustvo lekara Vojvodine, Srpskog lekarskog društva (Medicinski pregled), Vase Stajića 9, 21000 Novi Sad

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:

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), borders of 2.5 cm and font size 12pt. 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), material 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. It is to be followed by up to 10 Key Words from the list of Medical Subject Headings, MeSH of the American National Medical Library.

3. The expanded summary in English language. The summary in English should be the translation of the summary in Serbian, it should be structured in the same way as the Serbian summary, containing up to 250 words, without any abbreviations.

4. The text of the paper. The text of original studies must contain the following: introduction (with the clearly defined objective of the study), material 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.

– The text should be written in the spirit of Serbian language, without unnecessary abbreviations, whose first mentioning must be explained by the full term they stand for. Abbreviations should not be used in the title, summary and conclusion. Only commonly accepted abbreviations (such as DNA, MRI, NMR, HIV…) should be used. The list of abbreviations used in the text, together with the explanation of their meaning, is to be submitted at the last page of the manuscript.

– 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.

– No names, initials or case history numbers should be given.

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.

Material 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 problem mentioned in the introduction. Conclusions must be based solely on the author's own results, corroborating them. Avoid generalised and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

5. References. 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 organisation 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.

∗ *Acomputer file*

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

6. Attachments (tables, graphs, schemes and photographs). The maximum number of attachments allowed is six!

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

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

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