YU ISSN 0042-8450

# ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД

*Часопис лекара и фармацеута Војске Србије*

*Military Medical and Pharmaceutical Journal of Serbia*

# *Vojnosanitetski pregled*

**Vojnosanit Pregl 2011; September Vol. 68 (No. 9): p. 727-820.**

YU ISSN 0042-8450 vol. 68, br. 9, 2011.

# VOJNOSANITETSKI PREGLED

**Prvi broj *Vojnosanitetskog pregleda* izašao je septembra meseca 1944. godine**

**Časopis nastavlja tradiciju *Vojno-sanitetskog glasnika*, koji je izlazio od 1930. do 1941. godine**

**IZDAVAČ**
Uprava za vojno zdravstvo MO Srbije



**Adresa redakcije**: Vojnomedicinska akademija, Institut za naučne informacije, Crnotravska 17, poštanski fah 33–55, 11040 Beograd, Srbija. Telefoni: glavni i odgovorni urednik 3609 311, tehnički sekretar 3608 943, redakcija 3609 479 i 3609 179, pretplata 3608 997. Faks 2669 689. E-mail (redakcija): **vsp@vma.mod.gov.rs** i **vmavsp@hotmail.com**.

**Radove objavljene u „Vojnosanitetskom pregledu" indeksiraju: Science Citation Index Expanded (SCIE), Journal Citation Reports/Science Edition, Index Medicus (Medline), Excerpta Medica (EMBASE), EBSCO, Biomedicina Serbica. Sadržaje objavljuju Giornale di Medicine Militare i Revista de Medicina Militara. Prikaze originalnih radova i izvoda iz sadržaja objavljuje International Review of the Armed Forces Medical Services.**

Časopis izlazi dvanaest puta godišnje. Pretplate: žiro račun kod Uprave za javna plaćanja u Beogradu br. 840-941621-02 – VMA (za Vojnosanitetski pregled), PIB 102116082. Za pretplatu iz inostranstva obratiti se službi pretplate na tel. 3608 997. Godišnja pretplata: 4 000 dinara za građane Srbije, 8 000 dinara za ustanove iz Srbije i 150 € (u dinarskoj protivvrednosti na dan uplate) za pretplatnike iz inostranstva. Kopiju uplatnice dostaviti na gornju adresu.

Štampa Vojna štamparija, Beograd, Resavska 40 b.

YU ISSN 0042-8450 vol. 68 No. 9, 2011

# VOJNOSANITETSKI PREGLED

**The first issue of *Vojnosanitetski pregled* was published in September 1944**
**The Journal continues the tradition of *Vojno-sanitetski glasnik* which was published between 1930 and 1941**

**PUBLISHER**

Military Health Department, Ministry of Defence, Serbia



**Editorial Office**: Military Medical Academy, INI; Crnotravska 17, PO Box 33–55, 11040 Belgrade, Serbia. Phone: +381–11–3608–943; +381–11–3609–479, subscription 3608–997; Fax: +381–11–2669–689; E-mail: **vsp@vma.mod.gov.rs** and **vmavsp@hotmail.com**

**Papers published in the Vojnosanitetski pregled are indexed in: Science Citation Index Expanded (SCIE), Journal Citation Reports/Science Edition, Index Medicus (Medline), Excerpta Medica (EMBASE), EBSCO, Biomedicina Serbica. Contents are published in Giornale di Medicine Militare and Revista de Medicina Militara. Reviews of original papers and abstracts of contents are published in International Review of the Armed Forces Medical Services.**

The Journal is published monthly. Subscription: Account in Uprava za javna plaćanja in Belgrade. Giro Account No. 840-941621-02 – VMA (za Vojnosanitetski pregled), PIB 102116082. To subscribe from abroad phone to +381 11 3608 997. Subscription prices per year: individuals 4,000.00 Din, institutions 8,000.00 Din in Serbia, and foreign subscribers 150 €.

Printed by: Vojna štamparija, Beograd, Resavska 40 b.

# SADRŽAJ / CONTENTS

AKTUELNA TEMA / CURRENT TOPIC



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Svake godine, poslednje nedelje u septembru, obeležava se Svetski dan srca čiji je cilj da skrene pažnju svetske javnosti na kardiovaskularna oboljenja koja i dalje predstavljaju vodeći uzrok smrtnosti u svetu. Taj događaj prilika je da se istakne značaj preventivnih mera kojima se može značajno smanjiti rizik od pojave kardiovaskularnih bolesti i njihovih posledica (vidi Uvodnik, str. 731–2).

World Heart Day is globally celebrated in the last Sunday of September each year to inform people about cardiovascular diseases which are still the largest cause of death worldwide. The event also aims to promote preventive measures that can significantly reduce the risk of cardiovascular diseases and their consequences (see Editorial, pages. 731–2).

U V O D N I K

# Dan zaboravljenog SRCA

## Forgotten HEART Day

**Slobodan Obradović**

**Vojnomedicinska akademija,** Klinika za urgentnu medicinu, **Beograd, Srbija**

Radim kao kardiolog 12 godina u intenzivnoj nezi. Bila je nedelja, dežurstvo je proticalo sporo i nije se događalo ništa posebno. Oko 18 časova zvali su me iz Centra hitne pomoći da pogledam na ultrazvuku jednog mlađeg čoveka koji je izgledao loše, a nisu znali šta mu je. Od prošle noći oseća se užasno, imao je mučninu, povraćao na svakih 15-tak minuta i bio je jako malaksao. Dočekao sam ga u kabinetu za ultrazvuk. Imao je 46 godina, bio je kratko podšišan, nije bio gojazan, izgledao mi je mlađe. Bio je bled, teško je disao, orošen hladnim znojem, jedva se kretao i govorio. Rekao mi je da je advokat, da boluje od šećerne bolesti u poslednje 3 godine, da ima povišen holesterol, hipertenziju i da puši oko 40 cigareta dnevno. Nije uzimao nikakve lekove, nije imao vremena za sebe. Dok su mu pomagali da legne na levi bok, pogledao sam njegov EKG. Bio je u sinusnom ritmu, sa srčanom frekvencijom od 130 u minutu, uz blok desne grane i čudne promene repolarizacije. Na osnovu EKG-a nisam odmah shvatio šta se dešava, nisam očekivao da to može da se desi. Međutim, kada sam stavio sondu na njegove grudi bilo mi je sve jasno. Ceo prednji zid i septum nisu se kretali. Srce je radilo veoma brzo i veoma slabo. Ejekciona frakcija bila je oko 25%, protok preko mitralne valvule ukazivao je na restriktivni tip punjenja leve komore, tj. na tešku akutnu srčanu insuficijenciju. Bio je hipotenzivan, oko 100/50 mmHg. Nakon pregleda pitao je šta mu je i da li može da ide kući jer ima puno posla. Rekao sam mu da mora da ostane u bolnici. Dok su ga presvlačili izdvojio sam se sa njegovim bratom lekarom sa kojim je došao i koji je bio veoma zabrinut, i rekao mu da se radi o velikom infarktu prednjeg zida i da je u teškom stanju. Bio je veoma iznenađen i još zabrinutiji. Prošlo je 18 sati od početka tegoba. Prvi enzimi koji su ukazivali na infarkt srca bili su veoma visoki, kreatin kinaza oko 2 500 IU/L. Bilo je kasno za efikasnu reperfuzionu terapiju. Stavio sam mu centralni venski kateter i uključio dobutamin, dopamin, heparin i furosemid u kontinuiranoj infuziji. Popio je nekako četiri tablete klopidogrela i jednu tabletu aspirina. Bio je jako umoran. Stanje se tokom noći nije menjalo. U međuvremenu, razgovarao sam i sa njegovom suprugom, tj. bivšom suprugom jer već neko vreme ne žive zajedno, zvala je telefonom. Ujutro smo našeg bolesnika odveli u kateterizacionu salu. Stavili smo mu odmah intraaortnu balon pumpu i uradili koronarografiju. Prednja descedentna koronarna arterija bila je okludirana pre svih grana. Na cirkumfleksnoj arteriji i na grani desne koronarne arterije imao je suptotalne stenoze. Urađena je perkutana koronarna angioplastika na bifurkacionoj leziji prednje descedentne koronarne arterije i prve dijagonalne arterije i implantiran je dugačak stent. Infarktna arterija prikazala se cela, ali se usporeno praznila od kontrasta što je ukazivalo na opstrukciju u mikrocirkulaciji. Dobio je tri manja bolusa natrijum-nitroprusida intrakoronarno za lečenje nefunkcionalne mikrocirkulacije, a zatim je urađena i implantacija stenta na cirkumfleksnu koronarnu arteriju. Bili smo zadovoljni učinjenim i bolesnik je vraćen u koronarnu jedinicu. Sledećih nekoliko dana stanje se nije popravljalo. Naš bolesnik je bio slab, jedva je mogao da pokreće ruke i da govori. Bio je svestan i povremeno smo pričali. Imao je ćerkicu od devet godina koju je mnogo voleo. Brat je stalno dolazio. Često je satima sedeo pored postelje i masirao mu noge. Supruga je zvala svaki dan. Plasirali smo i drugi centralni venski kateter i uključili levosimendan, a zatim adrenalin u infuziji. Pritisak je bio sve niži. Započeli smo sa kontinuiranim ultrafiltracijama. Prestao je da mokri. Pošto više nije mogao da diše, stavili smo ga na respirator. Sve vreme smo se nadali da će se desiti čudo. Radili smo sve što možemo, sve što znamo, išli smo do kraja mogućnosti. Više nije bio svestan. Umro je nakon deset dana boravka na našoj klinici. Ja sam saopštio bratu da je kraj. Nije mogao da veruje.

*****

Četvrtak popodne, beskrajna ambulanta. Ušao je na vrata zbunjen i ozbiljan. Pogledao sam u knjižicu. Četrdesettri godine. Oslovio sam ga po imenu i pitao ga šta ga muči. Rekao je da ne zna, da se u poslednje vreme ne oseća dobro. Nema snage, nervozan je, pritiska ga u grudima. Mnogo radi, njegova advokatska kancelarija ima mnogo važnih klijenata. Mnogo puši, ne kreće se, iz kola u kancelariju. Već nekoliko meseci, kad mu brat izmeri pritisak, jer ga često boli glava, on je stalno 170/100. Uradio je laboratorijske analize. Bio je

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zabrinut kada je video brojke označene sa "Hi" iako mu one ništa ne znače. Holesterol 7,2, šećer u krvi 8,0.

Otac mu je umro u pedesetoj godini života od srca.

U početku sam mu svaku reč izvlačio iz usta. Izbegavao je direktan pogled, kao da se stidi što mi uopšte oduzima vreme. Kako je pregled odmicao bio je opušteniji, na licu se pojavio osmeh.

„Čini mi se da se poznajemo, samo ne mogu da se setim…", rekao je nekako usput.

Rekao sam mu da mu nalazi uopšte nisu dobri i da to moramo da promenimo.

Pregledao sam ga. Nalaz je, osim povišenog pritiska, bio normalan. EKG mu je, takođe, bio sasvim normalan, nije ništa skrivao.

Prepisao sam mu lekove. Simvastatin, nebivolol, ramipril, metformin, aspirin. Rekao sam mu da je veoma važno da ih uzima, objasnio sam mu šta koji od ovih lekova radi. Naglasio sam mu da mora da šeta.

„Moraš da prestaneš da pušiš!"

„Znam. Rešio sam!"

U ambulantu je utrčala devojčica plave kose. „Tata dođi!" Pomilovao ju je po glavi i rekao joj da ide kod mame. Ona ga nije poslušala, povukla ga je za ruku i izašli su zajedno. Nije se opirao.

„Kontrola za mesec dana," rekao sam.

„Hvala doktore, izvinite, vidimo se…."

*****

Juče smo zajedno prošetali oko Ade. Uživali smo u bojama, zvucima, mirisima, koracima… u dve devojčice sa plavom i kestenjastom kikom koje su na rolerima letele ispred nas…

Ne zaboravite svoje srce!

(Povodom Svetskog dana srca, 26. 09. 2011. godine)

ORIGINALNI ČLANCI

UDC: 611.133/.134::611.93]:616-073.432.19::616.13-004.6-07
DOI:10.2298/VSP1109733J

# Debljina intimomedijalnog kompleksa vertebralnih arterija: novi upotrebljivi parametar u proceni aterosklerotskog procesa?

## Intimomedial thickness of the vertebral arteries complex: a new useful parameter for the assessment of atheroclerotic process?

**Olivera Jovanikić*, Toplica Lepić†, Ranko Raičević†, Dragana Veljančić†, Andjelka Ristić‡, Branko Gligić‡**

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**Apstrakt**

**Uvod/Cilj.** Sastavni deo doplersonografskog pregleda krvnih sudova vrata je određivanje debljine intimomedijalnog kompleksa (IMK). Cilj ove studije bio je da se ispita odnos vrednosti debljine IMK na zajedničkoj karotidnoj i vertebralnoj arteriji da bi se utvrdilo da li vrednost debljine IMK merene na vertebralnim arterijama može biti primenjena u kliničkoj praksi. **Metode.** U randomizovanoj studiji preseka merena je debljina IMK kod 50 ispitanika oba pola (29 muškaraca i 21 žena), starosti od 18 do 79 godina [prosečna starost 52,4 (± 17,63) godine]. Svi ispitanici bili su zdravi na osnovu kliničkih i laboratorijskih pregleda. Merenja su vršena u periodu od januara 2006. do septembra 2008. godine. Dvodimenzionalnom ulstrasonografijom u B-modu zabeležene su vrednosti IMK na obe zajedničke karotidne arterije: rezultat jednog merenja dobijan je kao prosečna vrednost iz tri uzastopna merenja na tri različita mesta. Na obe vertebralne arterije debljina IMK merena je na prvom segmentu na oko 1,5 cm od prelaska u drugi segment (rezultati merenja debljine IMK na vertebralnoj arteriji dobijani su na isti način – prosek vrednosti iz tri puta na tri različita mesta). **Rezultati.** Kod 50 zdravih osoba izmerena vrednost IMK na zajedničkoj karotidnoj arteriji (IMK = 0,782 ± 0,248 mm) bila je po apsolutnoj vrednosti veća od vrednosti koja je izmerena na prvom segmentu vertebralne arterije (IMK = 0,585 ± 0,134 mm). Vrednosti IMK dobijene merenjem na ova dva različita mesta statistički su se visokoznačajno razlikovale ($t$ = 7,03, SD = 0,028, $p$ < 0,01). Koeficijent varijabilnosti vrednosti IMK u karotidnom slivu (CV = 34,4%) bio je veći od varijabilnosti vrednosti IMK u vertebralnom slivu (CV = 22,9%). Vrednosti IMK sa vertebralnih arterija statistički su visokoznačajno korelisale sa vrednostima IMK iz karotidnog sliva (koeficijent korelacije $r$ = 0,24 i $t$- = 2,48; $p$ < 0,02). Vrednosti dobijene na desnoj i levoj strani statistički se nisu razlikovale zbog čega su obrađene kao jedinstven skup. **Zaključak.** Vrednosti IMK na vertebralnoj arteriji predstavljaju još jedan, nezavisni parametar u doplersonografskom pregledu krvnih sudova vrata koji značajno koreliše sa vrednostima IMK na zajedničkoj karotidnoj arteriji. Varijabilnost ovog parametra je manja, a apsolutne vrednosti niže, nego u zajedničkoj karotidnoj arteriji. Zbog toga, ovaj parametar najverovatnije nije tako senzitivan. Sa druge strane, manja varijabilnost vrednosti IMK u vertebralnoj arteriji mogla bi ukazivati na veću specificnost povišenih vrednosti ovog parametra u predviđanju napredovanja ateroskleroze u odnosu na vrednosti merene na zajedničkoj karotidnoj arteriji.

**Ključne reči:**
**a. vertebralis; a. carotis communis; ateroskleroza; ultrasonografija, dopler; tunika intima; tunika media.**

**Abstract**

**Bacground/Aim.** An integral part of Doppler ultrasound examination of cervical blood vessels is determination of intimomedial thicknes (IMT) of the common carotid. The aim of the study was to estimate the relations between IMT of the common carotid and vertebral arteries in order to determine if the value of IMT obtained on the vertebral artery could be applied in clinical practice. **Methods.** We measured IMT in a randomized, prospective and cross-sectional study, performed on 50 persons both sexes (29 men and 21 women), at the age from 18 to 79 years (mean age 52.4 ± 17.63 years). All the persons were healthy, what was confirmed with clinical examination and laboratory analyses. Measurements were perfomed from January 2006 until September 2008. Intimomedial thickness was recorded by twodimensional ultrasonography in B-mode on both common carotid arteries: one value was obtained as average of three successeful measurements (measurements were perform on different places). We measured IMT on the first segment of both vertebral arteries, 1.5 cm proximal from the connection of the first and second segments (we got results of the measurement of IMT on the vertebral arteries in the same way: mean value from the three records). **Results.**

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The measured value of IMT on the common carotid arteries (IMT = 0.782 ± 0.248 mm), obtained from 50 healthy persons, was higher than that measured on the vertabral artery on the first segment (IMT = 0.585 ± 0.134 mm). The values of IMT after measurement on two different places were statistically highly different ($t$ = 7.03, SD = 0.028, $p$ < 0.01). Coefficient of variability of IMT values in carotid circulation (CV = 34.4%) was higher than that in vertebral circulation (22.9%). Values of IMT on vertebral arteries were in statistically significant correlation with those in carotid circulation ($r$ = 0.24 and $t$- = 2.48; $p$ < 0.02). There were no statistically significant difference between IMT measurement on the right and the left side so they were analysed as the same set **Conclusion.** Values of IMT on the vertebral arteries are one more undependent parameter of doplersonographic examination of cervical vessels, which significantly correlates with IMT values on common carotid artery. Variability of this parameter is lower, and absolute values lower than the same in the common carotid artery. Therefore, this parameter is probably not so sensitive. On the other hand, lower variability of IMT values on the vertebral artery might be of higher specificity for prediction of atherosclerotic progress by the increased values of this parameter than based on IMT values obtained on the common carotid arteries.

**Key words:**
**vertebral artery; carotid artery, common; atheroscerosis; doppler ultrasonography; tunica intima; tunica medica.**

## Uvod

Sastavni deo doplersonografskog pregleda krvnih sudova vrata je određivanje debljine intimomedijalnog kompleksa (IMK). Ovaj parametar se može meriti na zajedničkim ili unutrašnjim karotidnim arterijama ili na zidovima karotidnog bulbusa [1–9]. Dobro je definisan značaj ovog parametra za kliničku praksu, iako normalne vrednosti značajno variraju prema polu, starosti i etničkoj pripadnosti [10–12].

U randomizovanoj studiji preseka merene su vrednosti IMK u zajedničkim karotidnim arterijama i u vertebralnim krvnim sudovima. Pretpostavljeno je da su vrednosti IMK na drugom magistralnom krvnom sudu vrata (vertebralne arterije) nezavisne tj. drugačije, ali da se menjaju na isti način kao i u karotidnom slivu, jer na njih utiču isti metabolički, imunološki i sistemski faktori. Vrednosti IMK karotidnog sliva danas se koriste kao intermedijerni rezultat (*intermediate outcome*) u svakom ispitivanju ili istraživanju ateroskleroze [11, 13–16] zbog površinske lokalizacije, dimenzija i ograničene pokretljivosti karotidnih arterija, ali sve ove osobine poseduju i vertebralne arterije [17], a podatak se može dobiti prilikom istog pregleda.

Apsolutne vrednosti IMK podložne su varijaciji u zavisnosti od godina [12, 13], pola [18] i, naročito, od etničke pripadnosti [12, 13], zbog čega se normalne vrednosti IMK od strane različitih istraživača definišu za različita geografska područja [19–25].

Cilj ove studije bio je da se ispita odnos vrednosti debljine IMK na zajedničkoj karotidnoj i vertebralnoj arteriji da bi se utvrdilo da li vrednost debljine IMK merene na vertebralnim arterijama može biti primenjena u kliničkoj praksi.

## Metode

Ispitivanje je vršeno na ultrazvučnom dupleks aparatu marke Toshiba u B modu, sa smanjenjem dubine insonacije do granice od 5 cm radi postizanja uvećanja slike i ručnim merenjem debljine IMK. Korišćena je sonda frekvencije 7,5 MHz koja daje najbolju prostornu rezoluciju. U B-modu sonografije IMK kompleks dvostruka je linija koja se vidi na oba zida karotidne ili vertebralne arterije kada se arterija longitudinalno prikazuje [1, 2, 5, 21, 24, 25]. Dvostruka linija je hiperehogena i jedna od njih se graniči sa lumenom krvnog suda, a druga sa hipoehogenim slojem adventicije [1, 2, 5]. Beleži se debljina tog prvog, hiperehogenog sloja koji se neposredno graniči sa lumenom krvnog suda. Vrednost IMK se beleži na tri različita mesta i rezultat dobija kao prosečna vrednost iz tri zabeležena merenja [2].

Merenje je uvek vršeno na zadnjem zidu, u predelu gde nije bilo aterosklerotskih plakova, tri puta na delu krvnog suda dužine oko 1 cm. Merenje na zajedničkoj karotidnoj arteriji vršeno je na delu suda na oko 1,5–2,5 cm proksimalno od bifurkacije karotidne arterije, dok je na vertebralnoj arteriji merenje (jedan rezultat iz tri merenja) bilo vršeno na oko 1,5 cm pre drugog, spinalnog dela kičmene arterije.

Merenje je vršeno obostrano, a rezultati obrađeni kao nezavisni uzorci, iako veoma često postoje ispitivači koji smatraju da je potrebno određivati IMK samo na jednoj strani [26].

Od januara 2006. do septembra 2008. godine pregledano je i rezultati su zabeleženi kod 50 ispitanika oba pola: 29 muškaraca i 21 žene. Svi ispitanici, starosti od 18 do 79 godina, bili su zdravi na osnovu opšteg fizikalnog pregleda, pregleda očnog dna [27], zaključka kardiologa, endokrinologa, kao i laboratorijskih ispitivanja [28–32] i redovnog merenja arterijskog pritiska [33]. Određivani su, osim osnovnih biohemijskih parametara u krvi, obavezno i lipidni status, nivo fibrinogena, C-reaktivnog proteina, hematološki profil, kao i parametri značajni za hepatičnu i bubrežnu funkciju. Ispitanici su uvršteni u studiju, ukoliko su zadovoljavali sve prethodno navedene rezultate. Zbog raširenosti faktora koji favorizuju razvoj ateroskleroze nalaženje 50 ispitanika koji su imali normalne nalaze, naročito u sedmoj i osmoj deceniji života, zahtevalo je više od dve i po godine ispitivanja.

Rezultati su prikazani kao aritmetička sredina i standardna devijacija. Povezanost i disperzija rezultata ispitana određivanjem koeficijenata varijacije. Studentovim $t$ testom ispitana je značajnost razlike rezultata dobijenih na desnoj i levoj strani i na karotidnim i na vertebralnim arterijama. Na isti način provereno je da li vrednosti IMK dobijene u karotidnom i vertebralnom slivu pripadaju istom skupu, tj da li su to dva nezavisna klinička parametra.

**Rezultati**

U tabeli 1 prikazana je starosna i polna struktura ispitanika.

**Tabela 1**

**Starosna i polna struktura ispitanika**

| Starost (godine) | Broj ispitanika | | Ukupno |
|---|---|---|---|
| | muškarci | žene | |
| 18–30 | 4 | 2 | 6 |
| 31–40 | 4 | 3 | 7 |
| 41–50 | 4 | 6 | 10 |
| 51–60 | 4 | 4 | 8 |
| 61–70 | 5 | 3 | 8 |
| 71–80 | 8 | 3 | 11 |
| Ukupno | 29 | 21 | 50 |

**Prosečna starost: 52,4 ± 17,63 godine**

Sve dobijene vrednosti iz ukupno 100 merenja (nezavisno od strane na kojoj su vršena merenja) prikazane su u tabeli 2.

Prosečna vrednost IMK za karotidni sliv iznosila je 0,782 ± 0,248 mm, a za vertebralni sliv 0,585 ± 0,134 mm.

Vrednosti IMK dobijene merenjem na ova dva različita mesta statistički su se visokoznačajno razlikovale ($t$ = 7,03, SD = 0,028, nivo značajnosti $p < 0,01$).

Koeficijent varijacije za vrednosti IMK u karotidnom slivu bio je 34,4%, a u vertebralnom slivu 22,9%.

Vrednosti IMK dobijene na vertebralnim arterijama statistički su visokoznačajno korelisale sa vrednostima IMK iz karotidnog sliva (koeficijent korelacije $r$ = 0,24 i $t$- = 2,48; $p < 0,02$).

U tabeli 3 prikazane su vrednosti IMK u karotidnom i vertebralnom slivu sa leve strane.

Prosečna vrednost IMK u zajedničkoj karotidnoj arteriji sa leve strane u našoj populaciji bila je 0,792 ± 0,269 mm, a u levoj vertebralnoj arteriji 0,606 ± 0,143 mm.

Vrednosti IMK u karotidnom i vertebralnom slivu sa desne strane prikazane su u tabeli 4.

**Tabela 2**

**Vrednosti intimomedijalnog kompleksa (IMK) (prosečna vrednost iz tri merenja) u zajedničkoj karotidnoj i vertebralnoj arteriji sa obe strane zajedno**

| Debljina IMK (mm) | 0,3 | 0,4 | 0,5 | 0,6 | 0,7 | 0,8 | 0,9 | Ukupno |
|---|---|---|---|---|---|---|---|---|
| 0,4 | | 2 | 1 | 4 | 1 | 1 | | 9 |
| 0,5 | | 3 | | 5 | | 1 | | 9 |
| 0,6 | 1 | 3 | 2 | 3 | 1 | 2 | | 12 |
| 0,7 | | 3 | 11 | 5 | 2 | | | 21 |
| 0,8 | | 3 | 2 | 4 | 5 | 1 | | 15 |
| 0,9 | | 1 | 3 | 2 | 2 | 1 | | 9 |
| 1,0 | | | | 2 | 3 | 1 | 2 | 8 |
| 1,1 | | 1 | 1 | 3 | 1 | 3 | | 9 |
| 1,2 | | 2 | | 3 | | | | 5 |
| 1,3 | | | | | 1 | 1 | | 2 |
| 1,6 | | | | 1 | | | | 1 |
| Ukupno | 1 | 18 | 20 | 32 | 16 | 11 | 2 | 100 |

**U kolonama su vrednosti u vertebralnom, a redovima u karotidnom slivu**

**Tabela 3**

**Vrednosti intimomedijalnog kompleksa (IMK) u karotidnom i vertebralnom slivu sa leve strane**

| Debljina IMK mm | 0,3 | 0,4 | 0,5 | 0,6 | 0,7 | 0,8 | 0,9 | Ukupno |
|---|---|---|---|---|---|---|---|---|
| 0,4 | | 2 | 1 | 4 | 1 | 1 | | 9 |
| 0,5 | | 3 | | 5 | | 1 | | 9 |
| 0,6 | 1 | 3 | 2 | 3 | 1 | 2 | | 12 |
| 0,7 | | 3 | 11 | 5 | 2 | | | 21 |
| 0,8 | | 3 | 2 | 4 | 5 | 1 | | 15 |
| 0,9 | | 1 | 3 | 2 | 2 | 1 | | 9 |
| 1,0 | | | | 2 | 3 | 1 | 2 | 8 |
| 1,1 | | 1 | 1 | 3 | 1 | 3 | | 9 |
| 1,2 | | 2 | | 3 | | | | 5 |
| 1,3 | | | | | 1 | 1 | | 2 |
| 1,6 | | | | 1 | | | | |
| Ukupno | 1 | 18 | 20 | 32 | 16 | 11 | 2 | 100 |

**U kolonama su vrednosti u vertebralnom, a redovima u karotidnom slivu**

**Tabela 4**

**Vrednosti intimomedijalnog kompleksa (IMK) u karotidnom i vertebralnom slivu sa desne strane**

| Debljina IMK mm | 0,4 | 0,5 | 0,6 | 0,7 | 0,8 | 0,9 | Ukupno |
|---|---|---|---|---|---|---|---|
| 0,4 | 1 | 1 | 2 | 1 | | | 5 |
| 0,5 | 1 | | 2 | | | | 3 |
| 0,6 | 1 | 1 | | 1 | 1 | | 4 |
| 0,7 | 2 | 9 | 3 | | | | 14 |
| 0,8 | 2 | 2 | 1 | 4 | | | 9 |
| 0,9 | 2 | | 1 | 2 | | | 5 |
| 1,0 | | | 1 | 1 | | 1 | 3 |
| 1,1 | 1 | | 1 | 1 | | | 3 |
| 1,2 | 1 | | 2 | | | | 3 |
| 1,3 | | | | 1 | | | 1 |
| Ukupno | 11 | 13 | 13 | 11 | 1 | 1 | 50 |

**U kolonama su vrednosti u vertebralnom, a redovima u karotidnom slivu**

Prosečna vrednost IMK u desnoj karotidnoj arteriji kod naših ispitanika iznosila je 0,774 ± 0,226 mm, a u desnoj vertebralnoj arteriji 0,564 ± 0,121 mm.

Podaci sa leve i desne strane u našem ispitivanju nisu se značajnije razlikovali.

## Diskusija

Supklinička faza ateroskleroze je oštećenje endotela i postepeno difuzno zadebljanje IMK [14, 15, 34–40]. Informacija o ovom procesu se ne može dobiti angiografijom ili nuklearnom magnetnom rezonancom (MRI) [35, 36]. Dvodimenzijalni B-mod ultrasonografije omogućava praćenje ove faze. To je neinvazivno i moćno sredstvo u dijagnostikovanju, merenju i praćenju procesa ateroskleroze [2, 7, 12, 15, 26, 34, 37, 41–44].

Metoda merenja IMK na karotidnim arterijama definisana je početkom 90-ih godina XX veka [5, 6, 8, 19–24, 26]. Vodeća osobina ove metode je ponovljivost bez obzira što se danas citira najčešće 25 velikih studija posvećenih metodologiji merenja IMK na karotidnim arterijama. Iako normalne vrednosti značajno variraju prema polu [18], starosti [12, 13, 37, 45, 46], etničkoj pripadnosti [44–49], socioekonomskom statusu [50] veoma je dobro definisan značaj vrednosti debljine IMK za kliničku praksu. Nesumnjivo je dokazan značaj IMK kao bitnog prediktornog faktora u proceni stanja krvnih sudova u poremećajima metabolizma, dijabetesu, hiperholesterolemiji, hipertenziji [50–58]. Zadebljanja IMK su osnova za razvoj patoloških procesa u slučaju poremećaja hemostaznog sistema [31]. Vrednosti IMK dovode se u korelaciju sa pušenjem, anginom pektoris, infarktom miokarda, aneurizmom aorte, oboljenjem arterija donjih ekstremiteta. Ovaj parametar se smatra, ukoliko je povišen, dobrim prediktorom razvoja srčanog ili moždanog infarkta [44, 45, 49, 50].

Grupa ispitanika definisana je pretežno osobama starijeg životnog doba jer je poznato da se vrednost debljine IMK povećava od 0,01 do 0,03 mm godišnje, zbog čega populacija ispitanika pretežno starija od 45 godina, i naročito ako je više ispitanika muškog pola, daje preciznije rezultate.

Vrednosti IMK se najčešće određuju na zajedničkoj karotidnoj arteriji jer se bez obzira na široko variranje apsolutnih vrednosti, na ovom krvnom sudu dobijaju najhomogeniji rezultati [1, 2]. Iako se IMK može odrediti i na prednjem i na zadnjem zidu zajedničke karotidne arterije, zadnji zid se lakše prikazuje, zbog čega se češće i meri [1, 2].

U našoj studiji na 50 zdravih ispitanika određivanjem vrednosti IMK sa obe strane dobijeno je 100 vrednosti IMK u zajedničkoj karotidnoj arteriji, što je omogućilo dobijanje normalnih rezultata u ovoj populaciji i za zajednički karotidni i za vertebralni krvni sud.

Vrednosti desne i leve strane nisu se značajnije razlikovale iako postoje autori koji čvrsto zastupaju stanovište da ove vrednosti nikako nisu simetrične [26].

Dobijene vrednosti IMK u vertebralnom slivu, kao apsolutne vrednosti visokoznačajno su se razlikovale od onih u karotidnom slivu, što znači da su normalne vrednosti na vertebralnim arterijama drugačije i predstavljaju nezavisan parametar. Debljina IMK u vertebralnom slivu visoko značajno korelira sa promenama debljine u karotidnom slivu, što govori o specifičnosti ovog parametra, tj. da je njegovo povećanje sigurniji pokazatelj oštećenja endotela u aterosklerozi i da bi se on mogao primeniti u daljim ispitivanjima aktivnosti ateroskleroze. Niža varijabilnost IMK u vertebralnim arterijama ukazuje ili da ovaj parametar nije toliko senzitivan ili da je povećanje debljine IMK karotidnih arterija rezultat hemodinamskih uticaja na endotel karotida.

Uticaj svih drugih faktora na stanje endotela je praktično identičan jer je biohemijski sastav krvi isti i u vertebralnim i u zajedničkim karotidnim arterijama u paru podataka koji se poredi (vrednosti IMK beležene su u parovima kod istog bolesnika i tako su i obrađene).

## Zaključak

Metoda određivanja debljine je jednostavna, jeftina, ponovljiva, neškodljiva i visokoinformativna, a vertebralne arterije su malo pokretne, dostupne pregledu u distalnom delu V1 segmenta, a ukoliko nisu potpuno atrofične dovoljno su velike za određivanje IMK.

Dalja istraživanja detaljnijih promena vrednosti IMK na vertebralnim arterijama omogućila bi bolje definisanje ovog parametra koji se brzo i jednostavno može izmeriti u svakom rutinskom sonografskom pregledu krvnih sudova vrata.

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Primljen 18. V 2010.
Prihvaćen 12. IV 2011.

ORIGINAL ARTICLE

UDC:616.36:[613.25:611.95
DOI:10.2298/VSP1109739A

# Ultrasound measurement of visceral fat in patients with primary biliary cirrhosis

## Ultrasonografsko merenje visceralne masti kod bolesnika sa primarnom bilijarnom cirozom

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**Abstract**

**Background/Aim.** Primary biliary cirrhosis (PBC) is a progressive, chronic liver disease with elevated serum lipids, but it is unclear whether hyperlipidemia in PBC patients is associated with atherosclerosis. Metabolic syndrome promotes development of atherosclerotic cardiovascular disease related to abdominal type obesity and insulin resistance. The aim of our study was to assess abdominal adiposity in patients with PBC. **Methods.** The study included 40 patients with PBC and 50 healthy controls. Age, sex and anthropometric measurements (weight, height, body mass index and waist circumference) were registered for all patients and controls. We used ultrasonography to measure subcutaneous (SF) and visceral fat (VF) diameter, subcutaneous area (SA) and visceral area (VA), as well as perirenal fat diameter (PF). **Results.** Values of SF, VF and PF thicknesses in PBC patients were 19.23 ± 5.85 mm, 10.92 ± 3.63 mm, and 7.03 ± 1.82 mm, respectively. In controls these measurements were 22.73 ± 6.70 mm, 16.84 ± 5.51 mm and 10.50 ± 2.70 mm respectively. In PBC patients SA and VA were calculated to 983.64 ± 322.68 mm$^2$ and 403.64 ± 166.97 mm$^2$ and in controls 1124.89 ± 366.01 mm$^2$ and 720.57 ± 272.50 mm$^2$ respectrively. Significant difference was found for VF, VA and RF values. **Conclusions.** Considering that the amount of visceral fat plays an important role in development of metabolic syndrome and cardiovascular diseases, we concluded that the lower amount of visceral fat in PBC patients could be related to lower incidence of cardiovascular events, despite hyperlipidemia.

**Key words:**
**liver cirrhosis, biliary; subcutaneous fat, abdominal; obesity; caradiovascular diseases; risk factors; ultrasonography.**

**Apstrakt**

**Uvod/Cilj.** Primarna bilijarna ciroza (PBC) je progresivno hronično oboljenje jetre sa elevacijom lipida, ali nije sa sigurnošću potvrđeno da je ova hiperlipidemija udružena sa aterosklerozom. Metabolički sindrom dovodi do razvoja ateroskleroze i kardiovaskularnih oboljenja preko abdominalne gojaznosti i insulinske rezistencije. Cilj ovog istraživanja bio je da se proceni abdominalna gojaznost kod bolesnika sa PBC. **Metode.** Studija je obuhvatala 40 bolesnika sa PBC i 50 kontrolnih zdravih osoba. Analizirali smo uzrast, pol i antropometrijska merenja koja su uključivala telesnu masu, telesnu visinu, *body mass index* (BMI) i obim struka. Ultrasonografski, mereni su supkutana i visceralna mast i to njihova širina (SF – *subcutaneus fat*, VF – *visceral fat*) i površina (SA – *subcutaneus fat area*, VA – *visceral fat area*). Takođe, određivan je promer perirenalne masti (PF – *perirenal fat*). **Rezultati.** Vrednosti SF, VF i PF promera u ispitivanoj grupi sa PBC iznosile su 19,23 ± 5,85 mm, 10,92 ± 3,63 mm i 7,03 ± 1,82 mm redom. U kontrolnoj grupi ove vrednosti iznosile su 22,73 ± 6,70 mm, 16,84 ± 5,51 mm i 10,50 ± 2,70 mm redom. Izmerene vrednosti SA i VA bile su 983,64 ± 322,68 mm$^2$ i 403,64 ± 166,97 mm$^2$ kod bolesnika sa PBC, dok su u kontrolnoj grupi te vrednost iznosile 1124,89 ± 366,01 mm$^2$ i 720,57 ± 272,50 mm$^2$ redom. Statistički značajna razlika u vrednostima utvrđena je za VF, VA i RF. **Zaključak.** Kako količina visceralne masti ima značajnu ulogu u razvoju metaboličkog sindroma i kardiovaskularnih oboljenja, zaključili samo da je manja količina visceralne masti kod bolesnika sa PBC moguć razlog za manju učestalost kardiovaskularnih oboljenja u ovoj populaciji i pored hiperlipidemije.

**Ključne reči:**
**jetra, bilijarna ciroza; masno tkivo, potkožno, merenje; gojaznost; kardiovaskularne bolesti; faktori rizika; ultrasonografija.**

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**Introduction**

Primary biliary cirrhosis (PBC) is a progressive, chronic liver disease ultimately leading to hepatic failure and death if not treated by hepatic transplantation [1]. Serum lipids are often markedly elevated in PBC [2], but it is not clear if this hyperlipidemia is associated with accelerated atherosclerosis.

The risk of cardiovascular disease in PBC has been investigated in a few studies [2, 3] but an increase in related mortality was not demonstrated. There are few reports on the use of lipid lowering agents in PBC suggesting that lipid treatment could reduce LDL cholesterol and triglycerides leading to improved serum measures of hepatic function [4].

Metabolic syndrome (MS), that has received increased attention in the past few years, consists of multiple, interrelated risk factors of metabolic origin that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD). Most important of these underlying risk factors are abdominal obesity and insulin resistance. Other associated conditions include physical inactivity, aging, hormonal imbalance, and genetic or ethnic predisposition [5].

The measurement of abdominal obesity through waist circumference (WC) has been established as a simple, inexpensive and useful method for the diagnosis of abdominal obesity. Thus, WC has been proposed as a key element for the diagnosis of MS and its use suggested as a part of the routine general physical examination in clinical practice [6]. Moreover, WC correlates with visceral obesity, and in clinical studies, it has been associated with increased cardiovascular risk [7]. Ultrasonography (US) is a simple and reliable method for measuring both subcutaneous and visceral fat showing a strong correlation with both adiposities measured with computed tomography scan [8].

The aim of this study was to determine the amount of abdominal adipose tissue in PBC patients by anthropometry and ultrasonography measurements and to correlate these values with healthy control subject.

**Methods**

Study included 40 patients with PBC (4 males and 36 females), who underwent medical examination. The diagnosis was based on clinical features, laboratory tests, imaging diagnostics, and, whenever possible, on liver histology. All subjects gave written informed consent for participation in the study.

Anthropometric measurements included age, sex, weight, height, body mass index (BMI), and WC. Weight was measured to the nearest 0.1 kg with a calibrated physician's office scale, and the height to the nearest 1 mm with a wall-mounted height meter. Waist circumference was measured with a heavy-duty inelastic plastic fibre tape measure placed directly on the skin while the subject stood balanced on both feet, with the feet touching each other and both arms hanging freely. The measurement was taken immediately above the iliac crest and at the end expiration [9]. Sonography measurements were performed as described by Meriño-Ibarra et al. [10] using a linear-array probe (Toshiba Core Vision, Tokyo, Japan, 8 MHz PLF-805ST) in the supine position. It was kept perpendicular to the skin on the upper median abdomen, and longitudinal scan was done in the midpoint between the xyphoid and the navel along the alba line with regard to the surface of the liver, to be almost parallel to the skin. Subcutaneous fat thickness (SF) and area (SA) were measured on the xyphoumbilical line in both longitudinal and transverse views. Measurements were taken 3 times directly from the screen using electronic callipers at the inner edge of the skin and at the outer edge of the alba line and the fat muscle interfaces for area. Preperitoneal fat thickness or visceral fat thickness (VF) and area (VA) were measured in the same sites and views (Figures 1 and 2).


**Fig. 1 – Subcutaneous and visceral fat thickness measurement**


**Fig. 2 – Subcutaneous and visceral fat area measurement**

In this case, measurements were taken at the inner edge of the alba line and at the peritoneal line for thickness and area. Then mean values were calculated. All the subjects were asked to hold their breath during the examination. Special care was taken to keep the probe just touching the skin to prevent compression of the fat layers. A 3.75 MHz convex probe (PVF-375MT) was used to perform measurement of perirenal fat layer of the posterior right renal wall in the right posterior perinephric space [11]. All measurements were performed by a single physician.

Collected data were compared to 50 healthy subjects matched by sex and age.

Statistical analysis was performed using the SPSS software package (version 11.0). Mean values, SD, and ranges of the anthropometric and sonographic measurements were calculated. The Student's *t*-test was applied to assess the association of sonographic measures and the rest of studied variables. A *p*-value less than 0.05 was regarded as significant.

## Results

We have studied 40 patients known to have PBC (36 females, and 4 males) whose mean age was 55.65 ± 10.88 years. In the control group we studied 50 patients (46 females, and 4 males); mean age of the controls was 48.68 ± 7.87 years. Pearson's $\chi^2$ test failed to prove a significant difference in subject's gender between the studied group and the controls ($\chi^2 = 0.055$, $p > 0.05$). No significant difference regarding sex was found, i.e. the *t*-test failed to prove a significant differences between studied subjects and the controls (t = 2.492, $p > 0.05$).

Anthropometric and US measurements are shown in Table 1. Student's *t*-test did not reveal a significant difference in BMI, nor in diameter and subcutaneous fat area, i.e. a highly significant difference was found in correlation of perirenal fat thickens and parameters for visceral fat (diameter and visceral fat area) (Figures 3 and 4).

## Discussion

Primary biliary cirrhosis produces a marked increase in total cholesterol levels, primarily due to increased Lp-X [12]. Despite a marked hypercholesterolemia, excess mortality from cardiovascular diseases was not found in our PBC population [13]. This finding is in the agreement with other studies. It has made some investigators to conclude that PBC patients might even be protected from cardiovascular diseases [2, 14, 15]. Close patient follow-up in the same center, with immediate recording of any clinically relevant event, allowed us to reliably estimate for the first time the incidence of non-fatal cardiovascular events in PBC. The present data suggests that despite of high prevalence of hypercholesterolemia, patients with PBC are not exposed to a higher risk of cardiovascular events than the general population. Attentive PBC patient follow-up could explain differences in detection rates of clinical events between PBC patients and general population and account for slightly higher incidence of coronary events that appear to be of borderline significance in PBC [13].

It is shown that mesenteric fat thickness is an independent determinant of metabolic syndrome in apparently healthy Chinese subjects, with an odds ratio of 1.35 for every 1 mm increase, at least within the observed range of mesenteric fat thickness. The discriminating cut-off point of 10 mm indicates the presence of metabolic syndrome and identifies subjects with increased intima-media thickness. Hypotheses

**Table 1**

**Anthropometric and ultrasound measurements of patients with primary biliary cirrhosis (PBC) and controls**

| Parameters | $\bar{x} \pm SD$ | | *t* | *p* |
|---|---|---|---|---|
| | The patients with PBC (n = 40) | The control subject (n = 50) | | |
| Body mass index (kg/m$^2$) | 25.386 ± 2.753 | 26.540 ± 3.543 | -1.195 | 0.239 |
| Waist circumference (mm) | 90.08 ± 9.08 | 90.76 ± 12.74 | -0.203 | 0.840 |
| Perirenal fat (mm) | 7.03 ± 1.82 | 10.4960 ± 2.7053 | -4.902 | 0.000 |
| Subcutaneus fat (mm) | 19.23 ± 5.85 | 22.73 ± 6.70 | -1.841 | 0.072 |
| Subcutaneus fat (mm$^2$) | 983.64 ± 322.68 | 1124.89 ± 366.01 | -1.355 | 0.183 |
| Visceral fat (mm) | 10.92 ± 3.63 | 16.84 ± 5.51 | -4.137 | 0.000 |
| Visceral fat (mm$^2$) | 403.64 ± 166.97 | 720.57 ± 272.50 | -4.556 | 0.000 |

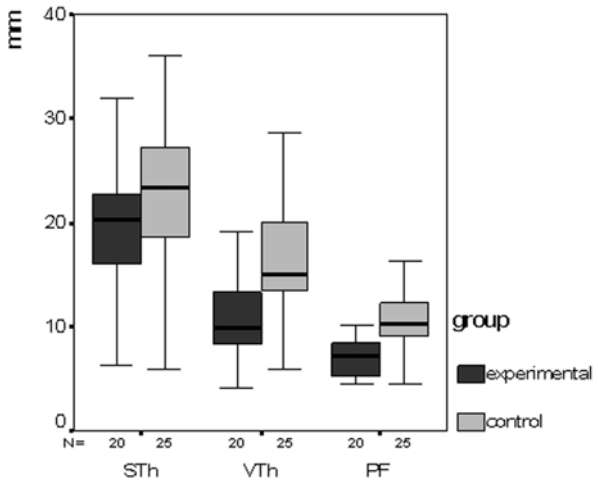


**Fig. 3 – Difference in diameter of subcutaneous, visceral and perirenal fat thickness (STh – subcutaneus fat, VTh – viceral fat, PR – perirenal fat)**

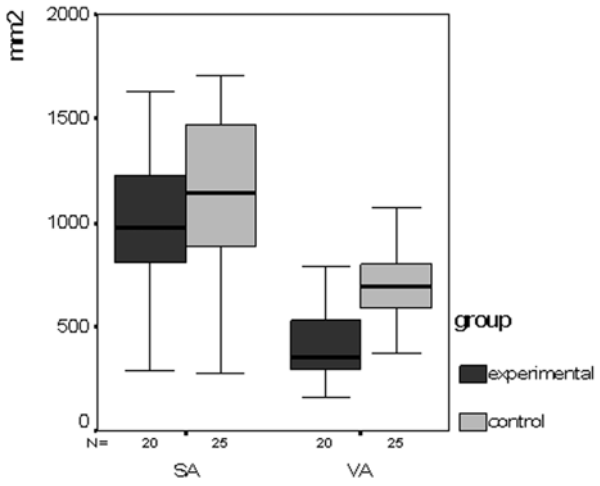


**Fig. 4 – Difference between subcutaneous and visceral fat area (SA – subcutaneus fat area, VA – visceral fat area)**

relating central adiposity to the metabolic syndrome focus on the newly emerging evidence that adipose tissue (particularly visceral adipose tissue) is a source of various factors, including free fatty acids, and tumor necrosis factor-alpha (TNF-α) that impair insulin action in skeletal muscle. In addition, adiponectin (adipose specific collagen-like molecule), has been found to have antidiabetic, antiatherosclerotic and antiinflammatory functions [16]. Excessive adipose tissue is associated with a decreased production of adiponectin which may impair insulin sensitivity [17]. Measurement of mesenteric fat thickness may potentially be developed into an alternative tool to identify subjects at risk for cardiovascular diseases [18].

Several imaging methods have been proposed for estimation of visceral adipose tissue Recent advances in imaging techniques and an understanding of differences in molecular biology of different adipose tissue depots have been reported. Computed tomography (CT) and especially Magnetic Resonance Imaging (MRI), the gold standard technique, provide methods to non-invasive estimate visceral adipose tissue safely and accurately [19–21]. Unfortunately, both MRI and CT are high-cost technologies, and CT requires radiation exposure. In addition, a great variability in the precise definition of adipose tissue compartments by CT and MRI measurements is found in clinical studies [22]. The measurement of visceral fat volume using US could be as effective as CT. This method should be used in clinical settings due to its low cost, no side effects and technical suitability [23, 24].

Analysing the data gathered by US, as non-invasive, inexpensive, and non-ionization method, we found that despite the lack of significant differences of BMI, PBC patients have smaller amount of perirenal and visceral fat, as well as visceral fat area compared to controls. Other measurements of fat tissues (diameter and surface of subcutaneous fat) in the PBC patients are lower compared to the control subjects, but the observed difference was not significant.

**Conclusion**

Using ultrasonography as a reliable method for measurement visceral fat amount and taking into account importance of visceral fat in development of metabolic syndrome and cardiovascular diseases, we conclude that patients with primary biliary cirrhosis have lower amount of visceral fat, and probably due this phenomenon a lower incidence of cardiovascular diseases, despite a marked hypocholesterolemia.

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Received on January 12, 2010.
Accepted on May 19, 2010.

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UDC: 616-072.1::616.348/.351-006-089.81
DOI:10.2298/VSP1109744N

# Endoskopska mukozna resekcija kolorektalnih tumora – naša prva iskustva

## Endoscopic mucosal resection of colorectal tumors – our first experience

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**Apstrakt**

**Uvod/Cilj.** Endoskopska mukozna resekcija (EMR) ili mukozektomija je interventna procedura za minimalno invazivno endoskopsko uklanjanje benignih i malignih tumora digestivnog trakta. Mukozektomijom se uklanjaju zaravnjene i sesilne neoplazme, rani kolorektalni karcinomi (CRC) ograničeni na mukozu ili submukozu i tumori koji se lateralno šire. Cilj ovog rada bio je da se pokažu naša prva iskustva u primeni ove metode u svakodnevnoj praksi, koja se odnose na kompletnost i efikasnost procedure, stopu komplikacija i incidenciju rekurentnih adenoma. **Metode.** Prospektivnom studijom obuhvaćena su 44 bolesnika oba pola, kod kojih je metodom EMR uklonjen 51 kolorektalni adenom. **Rezultati.** Kod 43 bolesnika urađena je jedna mukozektomija, a kod jednog bolesnika 8 mukozektomija. U svim procedurama postignuta je potpuna resekcija tumora. U 36 (68,62%) procedura urađena je *„en block"* resekcija, a u 15 (31,37%) *„piece meal"* („deo po deo") resekcija. Kod 20 (45,45%) bolesnika otkriveni su sinhroni kolorektalni tumori (benigni ili maligni). Najveći broj adenoma bio je sa displazijom umerenog (30 ili 58.82%), i teškog (9 ili 17,64%) stepena. Intramukozni CRC otkriven je kod šest (11,77%) adenoma. Kod pet (11,36%) bolesnika mukozektomirano je šest intramukoznih CRC. Uklonjeno je 37 (72,54%) uznapredovalih adenoma. U vremenskom periodu od 6 do 30 meseci od mukozektomije recidivirala su tri (5,88%) adenoma. Krvarenje kao komplikacija mukozektomije verifikovano je kod jednog (2,2%) bolesnika. **Zaključak**. EMR je sigurna i bezbedna za uklanjanje zaravnjenih i sesilnih adenoma, kao i ranih CRC, i predstavlja rutinsku endoskopsku proceduru u svakodnevnoj praksi interventnog endoskopiste.

**Ključne reči:**
**kolorektalne neoplazme; endoskopija, gastrointestinalna; lečenje, ishod.**

**Abstract**

**Background/Aim.** Endoscopic mucosal resection (EMR) or mucosectomy is an interventional procedure for minimal invasive endoscopic removal of benign and malignant digestive tract tumors. Mucosectomy removes flat and sessile neoplasms, early colorectal cancer (CRC) confined to mucosa or submucosa and lateral spreading tumors. The aim of the study was to show our first experience in application of this procedure in everyday practice in regarding completeness and efficacy of the procedure, complication rate and incidence of recurrent adenomas. **Methods.** In the prospective study 51 colorectal adenomas were removed in 44 patients by EMR. **Results.** Single mucosectomy was done in 43 patients, while multiple (8) in one patient. Complete resection was obtained in all procedures. In 36 (68.62%) procedures „en block" resection was done, but in 15 (31.37%) procedures „piece meal" resection was performed. Synchronous colorectal tumors (benign or malignant) were detected in 20 (45.45%) patients. Moderate dysplasia was found in 30 (58.82%) adenomas, but high grade dysplasia in 9 (17.64%) of adenomas. Intramucosal CRC was detected in 11.77% of adenomas. A total of 37 (72.54%) advanced adenomas were removed. There were 3 (5.88%) of recurrent adenomas, 6–30 months after the EMR. Only one (2.2%) case of post procedure bleeding was observed. **Conclusion:** EMR is a safe and efficious method for removal of flat, sessile adenomas, as well as early CRC. EMR is a routine endoscopic procedure in everyday practice of interventional endoscopist.

**Key words:**
**colorectal neoplasms; endoscopy, gastrointestinal; treatment outcome.**

### Uvod

Većina karcinoma debelog creva (CRC) nastaje malignom transformacijom adenoma kroz proces aktivacije onkogena i inaktivacije tumor supresornih gena (*adenoma – carcinoma sequence*) [1]. Polipektomija kolorektalnih adenoma prevenira nastanak CRC i smanjuje incidenciju karcinoma i do 90% od očekivane [2, 3].

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Endoskopska mukozna resekcija (EMR) ili mukozektomija i endoskopska submukozna disekcija su razvijene za minimalno invazivno endoskopsko uklanjanje benignih i malignih tumora digestivnog trakta [4]. Ova procedura predstavlja glavni terapijski napredak u tretmanu gastrointestinalnih malignih tumora. Prvi put je uvedena u Japanu pod nazivom „*strip biopsy*" kao endoskopska dijagnostička tehnika za karcinom želuca [5]. Endoskopska mukozna resekcija brzo postaje terapijski modalitet kao alternativa hirurškoj resekciji za terapiju ranih karcinoma u svim segmentima digestivnog trakta [6]. Mukozektomijom se uklanjaju zaravnjene i sesilne neoplazme (prema Pariskoj klasifikaciji tipovi I i 0-II), rani CRC ograničeni na mukozu ili submukozu i tumori koji se lateralno šire [7]. Endoskopska mukozna resekcija se koristi za uklanjanje tumorskih promena prečnika do 2 cm ili za uklanjanje metodom „deo po deo" (*piece meal metoda*) većih tumora. Ovom procedurom se odstranjuje deo zida kolorektuma koji sadrži mukozu, *muscularis* mukozu i, delimično ili kompletno, submukozni sloj. Pored uklanjanja benignih adenoma različitog stepena atipije, mukozektomija omogućava lečenje ranog CRC gde je rizik od metastaza u limfne žlezde minimalan. Mukozektomija obezbeđuje i adekvatan tkivni materijal za precizni patološki „*staging*" [8]. Petogodišnje preživljavanje bolesnika sa invazivnim CRC iznosi oko 40% [9], dok je petogodišnje preživljavanje bolesnika sa ranim CRC (karcinom ograničen na mukozu ili submukozu, bez obzira na regionalne limfne žlezde) do 97% [10], što potvrđuje značaj mukozektomije u snižavanju mortaliteta bolesnika sa CRC.

Cilj ovog rada bio je da prikaže naša prva iskustva u primeni ove metode u svakodnevnoj praksi, koja se odnose na kompletnost i efikasnost procedure, stopu komplikacija i incidenciju rekurentnih adenoma.

## Metode

U Klinici za gastroenterologiju i hepatologiju Kliničkog centra Niš, u periodu od 1. oktobra 2006. godine do 30. septembra 2008, metodom endoskopske mukozne resekcije, tehnikom ubrizgaj i seci (*inject and cut*), uklonjen je 51 kolorektalni adenom kod 44 bolesnika oba pola, starosti 30–83 godine. Kolonoskopije su obavljene fiberoptičkim kolonoskopima i videokolonoskopima marke Olympus i Pentax. Fiziološki rastvor adrenalina u koncentraciji 1 : 10 000 ubrizgavan je u bazu sesilne ili zaravnjene (*flat*) polipoidne promene u volumenu od 4 do 20 mL dok nije postignuto adekvatno izdizanje tumorske promene, a zatim je polipoidna promena uklanjana heksagonalnom omčom, postupkom standardne polipektomije uz pomoć elektrohirurške jedinice. Procena endoskopske resektabilnosti bazirala se na postojanju znaka „odizanja" (*lifting*) nakon submukozne injekcije. Veličina polipa određivana je pre postupka za elevaciju, na osnovu poznate veličine otvorenih bioptičkih kliješta. Sinhroni polipi su uklonjeni metodom polipektomije, a širokobazne tumorske promene sa makroskopkim karakteristikama malignih tumora su biopsirane. Po završetku mukozektomije kod svih bolesnika je potvrđeno kompletno uklanjanje polipoidne promene. Materijal je poslat Centru za patologiju gde su primenjene standardne histološke metode bojenja (hematoksilin i eozin). Adenomi veličine ≥ 10 mm, sa viloznom strukturom, ili displazijom ozbiljnog stepena klasifikovani su kao uznapredovali adenomi (*advanced colorectal adenoma-ACA*). Nakon mukozektomije bolesnici su endoskopski praćeni u vremenskim intervalima od tri do šest meseci od mukozektomije u zavisnosti od patohistološkog nalaza uklonjene promene.

Podaci su obrađeni u programskom paketu SPSS verzija 15.0. Korišćeni su Studentov *t*–test i Pearson-ov $\chi^2$ test; $p < 0.05$ je korišćen kao prihvatljivi nivo značajnosti.

## Rezultati

Od 44 bolesnika, muškaraca je bilo 29, a žena 15. Prosečna starost bolesnika iznosila je 62,1 godinu. Dijagnostikovano je ukupno 79 tumora debelog creva (tabela 1).

**Tabela 1**

**Histološka struktura tumora debelog creva**

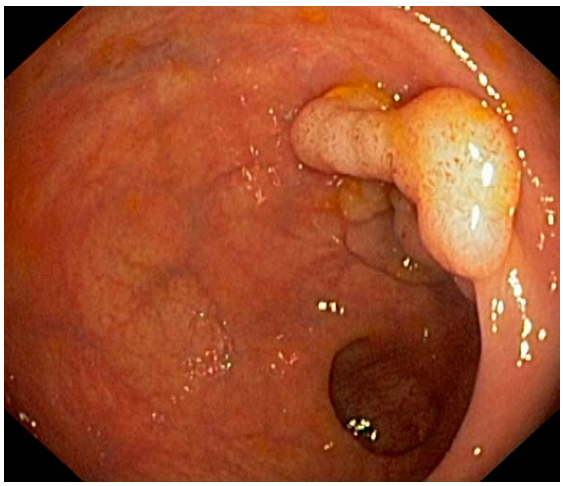
| Histološka struktura | Broj (%) |
|---|---|
| Tubularni adenom | 23 (29,11) |
| Tubulovilozni adenom | 41 (51,90) |
| Vilozni adenom | 8 (10,12) |
| Kolorektalni karcinomi (CRC) | 3 (3,80) |
| Hiperplastični polip | 2 (2,53) |
| Fibrom | 1 (1,27) |
| Karcinoid | 1 (1,27) |
| Ukupno | 79 (100) |

Dominirali su adenomi sa učestalošću od 91,13%, što je statistički značajno više od svih ostalih dijagnostikovanih tumora, $p < 0,001$. Tubulovilozni adenomi dominirali su u grupi adenoma (51,9%), što je bilo statistički značajno češće u odnosu na tubularne ($p < 0,05$) i vilozne adenome ($p < 0,01$).

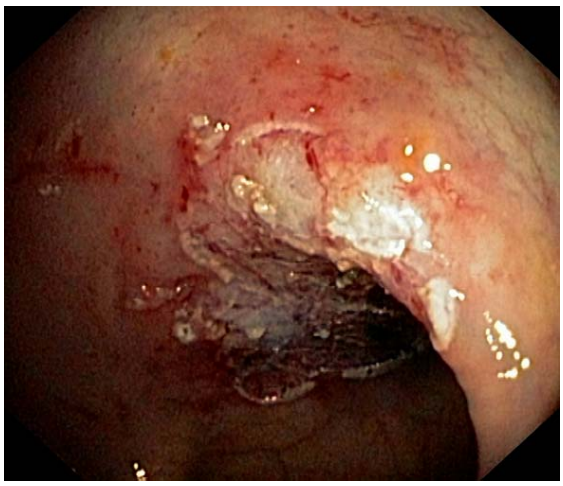
Kod 43 bolesnika urađena je jedna mukozektomija, a kod jednog bolesnika urađeno je osam mukozektomija. U svim procedurama postignuta je potpuna resekcija tumora. Kod 36 (68,62%) procedura urađena je „*en block*" resekcija, a kod 15 (31,37%) „deo po deo" resekcija (slike 1 i 2). Kod 24 (54,55%) bolesnika, kod kojih je učinjena mukozektomija, totalnom kolonoskopijom nije otkriven drugi tumor, dok su kod 20 (45,45%) bolesnika otkriveni sinhroni tumori (benigni ili maligni).

Veličina mukozektomiranih polipa bila je 5–40 mm, prosečno 12,8 mm, dok je veličina polipektomiranih sinhronih polipa 4–16 mm, prosečno 7,6 mm, što je statistički značajna razlika, $p < 0,05$. Lokalizacija i histološka struktura mukozektomiranih polipa prikazane su u tabeli 2. Predominiraju tubulovilozni adenomi (29 ili 56,86%), a zatim tubularni adenomi (15 ili 29,42%). Tubulovilozni adenomi statistički su značajno češća histološka struktura mukozektomiranih tumora od viloznih ($p < 0,001$) i tubularnih adenoma ($p < 0,05$).

Najveći broj tubularnih, tubuloviloznih i viloznih adenoma uklonjeno je u rektumu. U odnosu na samu lokalizaciju, tubulovilozna struktura dominira u rektumu, sigmi i



**Sl.1 – Tumor rektuma pre resekcije „deo po deo"**



**Sl.2 – Resekcija tumora „deo po deo"**

**Tabela 2**

**Distribucija mukozektomiranih polipa prema lokalizaciji i histološkoj strukturi**

| Histološka struktura | Rektum | Sigma | Descend. | Transverz. | Ascendens | Cekum | Ukupno |
|---|---|---|---|---|---|---|---|
| Tubularni | 6 (40%) | 5 (33,33%) | 1 (6,67%) | 1 (6,67%) | 2 (13,33%) | 0 (0%) | 15 (100%) |
| Tubulo-viloz | 14 (48,27%) | 10 (34,48%) | 0 (0%) | 0 (0%) | 4 (13,79%) | 1 (3,46%) | 29 (100%) |
| Vilozni | 6 (85,71%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (14,29%) | 0 (0%) | 7 (100%) |
| Ukupno | 26 | 15 | 1 | 1 | 7 | 1 | 51 |

ascendentnom kolonu, međutim razlika je statistički značajna samo u rektumu ($p < 0,05$). Najveći broj uklonjenih adenoma bio je sa displazijom umerenog stepena (30 ili 58,82%), a zatim sa displazijom teškog stepena (9 ili 17,64%), ($p < 0,05$). Displazija lakog stepena i intramukozni CRC otkriveni su kod 6 (11,77%) adenoma. Kod pet (11,36%) bolesnika mukozektomirano je šest intramukoznih CRC.

Uklonjeno je 37 (72,54%) uznapredovalih adenoma. Najveći broj bolesnika imao je sinhrone tumore u udaljenim segmentima (40%) od segmenta inicijalnog tumora. Četiri bolesnika imalo je sinhrone tumore u rektumu i ascendensu, dva u rektumu i cekumu, a po jedan u sigmi i ascendensu i sigmi i cekumu. U istim segmentima su verifikovani sinhroni tumori kod sedam (35%) bolesnika, i to u četiri bolesnika u sigmi, dva u ascendensu i kod po jednog u rektumu i ascendentnom kolonu. U susednim segmentima nađeni su sinhroni tumori kod pet (25%) bolesnika, a najčešće dijagnostikovana je kombinacija rektuma i sigme (četiri bolesnika). Kod svakog četvrtog mukozektomiranog bolesnika proksimalno od mesta intervencije otkriveni su uznapredovali tumori: osam ACA, tri uznapredovala CRC i 1 karcinoid. Kod više od polovine (55%) bolesnika sa sinhronim tumorima otkriveni su proksimalni uznapredovali tumori: u udaljenim segmenima kod pet bolesnika (kod dva bolesnika kombinacija rektum i cekum, kod dva bolesnika kombinacija rektum i ascendens i kod jednog sigma i cekum), susednim kod dva (rektum i sigma) i u istim segmentima kao i mukozektomirani adenomi kod četiri bolesnika (sigma kod tri bolesnika, ascendens kod jednog bolesnika). Dva uznapredovala CRC verifikovana su u neposrednoj blizini mukozektomiranih adenoma (sigma), dok je kod jednog bolesnika uznapredovali CRC bio u udaljenom segmentu (sigma i ascendens).

U vremenskom periodu od 6 do 30 meseci od mukozektomije recidivirala su tri (5,88%) adenoma, tubulovilozne i vilozne strukture sa srednje teškom i teškom displazijom, prečnika preko 10 mm, 30 mm i 40 mm, ponaosob. Kod dva bolesnika rekurentni adenom bio je sa displazijom istog stepena kao i inicijalni adenom, a kod jednog bolesnika sa displazijom ozbiljnijeg stepena od inicijalnog adenoma. Rekurentni adenomi ponovo su uklonjeni metodom mukozektomije i 12 meseci nakon intervencije nije bilo ponovljenog adenoma. Svi rekurentni adenomi bili su u rektumu i kod bolesnika kod kojih je rađena mukozektomija po metodi „deo po deo".

Krvarenje nakon mukozektomije potvrđeno je kod jednog (2,2%) bolesnika posle uklanjanja rektalnog adenoma. Krvarenje je zaustavljeno injekcionom hemostazom rastvorom adrenalina i primenom dva hemoklipsa.

## Diskusija

Endoskopska mukozna resekcija danas je rutinska interventna procedura za uklanjanje širokobaznih polipoidnih i zaravnjenih adenoma sa različitim modifikacijama tehnike, ali i ranih karcinoma u svim segmentima digestivnog trakta [11]. Metoda je prevashodno razvijena da omogući dobijanje velikih isečaka za patohistološko ispitivanje i za uklanjenje velikih adenoma. Prvi put opisali su je Deyhle i sar. [12] i Karita i sar. [13, 14] i vrlo brzo je izmenila lečenje sesilnih i zaravnjenih gastrointestinalnih tumora. Procedura uključuje klasične principe standardne polipektomije sa omčom, kombinovane sa submukoznom injekcijom rastvora da

bi se učinilo presecanje i uklanjanje promene koja je lokalizovana u dubokom sloju mukoze ili u submukozi.

U prednosti je u odnosu na alternativnu hiruršku intervenciju za uklanjanje adenoma sa *ca in situ* i ranih karcinoma kolorektuma sa invazijom submukoze zbog manjeg proceduralnog morbiditeta i mortaliteta [15].

Osnova EMR tehnike leži u dubokoj submukoznoj injekciji fiziološkog rastvora da bi se zadebljao zid kolorektuma na mestu polipektomije, kako bi omogućio duboku resekciju submukoze bez uzrokovanja transmuralne opekotine ili perforacije zida kolorektuma. Ubrizgavanje rastvora u submukozu, takođe, tamponira arteriju koja hrani polip i smanjuje postpolipektomno krvarenje, potpomaže vazospazam, povećava tkivni lividitet i električnu provodljivost na bazi polipa, što olakšava elektrokauterizaciju. Efekat submukozne injekcije je vidljiv tokom kolonoskopije. Promena koja se izdigne tokom ubrizgavanja rastvora je podesna za EMR. Polipoidna promena koja se ne izdigne je nepodesna za EMR, a postoji velika verovatnoća da je prisutan invazivni karcinom [8]. Komplikacije EMR se saopštavaju kod 9.6–25% slučajeva nakon procedure [16–18]. Opisuju se krvarenje i sindrom transmuralne opekotine [16], a retko i perforacije [17, 18]. U skoro svim slučajevima moguće je konzervativno rešavati komplikacije. Hemostaza klipsevima, nekada u kombinaciji sa rastvorom adrenalina, je sigurna i bezbedna metoda za rano ili zakasnelo krvarenje. U našoj studiji, rano krvarenje je bila jedina komplikacija EMR (2,2%) i zaustavljeno je kombinacijom hemoklipsa i rastvora adrenalina. Niža stopa krvarenja u odnosu na druge studije [16–18] može se objasniti selekcijom bolesnika jer je u našoj studiji bilo manje bolesnika sa ranim CRC.

Metoda EMR urađena je kompletno u svim procedurama. U literaturi se saopštavaju kompletne ekscizije nakon EMR u rasponu 75–98,1% slučajeva [16, 19–22]. Stopa uspešnosti EMR zavisi od veličine tumora i dubine invazije. Prihvaćeno je da je promene preko 30 mm teško ukloniti „*en block*“, pa je često potrebna resekcija „deo po deo“ [17, 18]. „*En block*“ resekcija je postignuta kod 73,1% polipa manjih od 30 mm i kod 15,4% polipa većih od 30 mm [16]. Prosečna veličina uklonjenih tumora bila je 12,8 mm, što je značajno niže od saopštenih [16, 19–22]. Pored toga, u našoj seriji bilo je samo šest (11,76%) intramukoznih CRC, što objašnjava 100% stopu kompletiranja interventne procedure.

Stopa recidiva sesilnih adenoma nakon EMR iznosi 0–40%. Teško je uporediti različite serije zbog varijacija veličine polipa i dužine perioda kontrole. Verovatno je da bolesnici sa većim adenomima imaju veći rizik od razvoja novih polipa [23–25]. Povećani rizik od recidiva nakon EMR zapažen je kod bolesnika sa polipima većim od 35 mm [26]. Od tri recidivantna adenoma nakon EMR jedan je prečnika 40 mm.

Argon-plazmatski koagulator redukuje učestalost recidivantnih adenoma za 50% nakon upotrebe zbog rezidualnog tkiva nakon mukozektomije [27]. Zlatanic i sar. [28] saopštavaju stopu recidiva od 100% nakon EMR bez argon-plazmatske koagulacije, u poređenju sa manje od 50% kada je argon-plazmatska koagulacija dopunila EMR. Regula i sar. [29] sproveli su kompletnu eradiciju adenoma kod 90% slučajeva kada su EMR kombinovali sa argon-plazmatskom koagulacijom. U našem radu argon-plazmatsku koagulaciju nismo koristili, već smo rezidualno tkivo uklanjali termokoagulacijom.

Vodiči za praćenje bolesnika nakon polipektomije kolorektalnih polipa primenjuju se i nakon EMR [30]. Savetuje se kolonoskopija 1–3 meseca nakon EMR u proceni rezidualnog tkiva, a u zavisnosti od rizika od razvoja metahronih ACA, histologije, veličine i broja adenoma i u zavisnosti da li je učinjena „*en block*“ ili resekcija „deo po deo“. Nakon kompletne resekcije, kolonoskopije treba raditi: na 10 godina nakon EMR hiperplastičnih polipa; na 5–10 godina nakon EMR 1–2 mala tubularna adenoma sa niskostepenom displazijom; na tri godine nakon EMR kod bolesnika sa 3–10 adenoma ili bolesnika sa uznapredovalim adenomom (kada je urađena „*en block*“ resekcija); za bolesnike sa više od 10 adenoma pre navršene 3 godine; bolesnike sa sesilnim adenomom uklonjenim metodom „deo po deo” treba kontrolisati nakon 1, 3 i 5 godina; nakon EMR tumora sa lateralnim širenjem, kontrolne kolonoskopije treba raditi češće. Kod bolesnika sa rektalnim lezijama treba raditi češće kolonoskopije, svakih 3–6 meseci, u prve 2–3 godine od EMR. Kod svih bolesnika sa resekcijom „deo po deo“ prva kolonoskopija urađena je nakon 1–3 meseca od EMR, u zavisnosti od patohistološkog nalaza resekovanog tumora, a zatim nakon 6 meseci do isteka 2 godine, a zatim jednom godišnje. Kod bolesnika sa „*en block*” resekcijom prva kolonsokopija rađena je nakon 3–6 meseci, takođe, u zavisnosti od patohistološkog nalaza, zatim na 6 meseci do isteka 2 godine od intervencije, zatim jednom godišnje.

## Zaključak

Metoda EMR je sigurna i bezbedna, minimalno invazivna terapijska procedura koja se rutinski izvodi kod bolesnika sa sesilnim i zaravnjenim adenomima kolorektuma, kao i kod bolesnika sa ranim CRC i tumorima sa lateralnim širenjem.

## Zahvalnica

Rad je delimično finansiran iz projekta III44004 od strane Ministarstva za Nauku i Obrazovanje Republike Srbije.

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Primljen 22. I 2010.
Revidiran 30. III 2010.
Prihvaćen 31. III 2010.

ORIGINALNI ČLANAK

UDC: 616.61-008.6::616.61-78]:616.155.194-08
DOI:10.2298/VSP1109749K

# Uticaj nivoa hemoglobina i visine doze rekombinantnog humanog beta eritropoetina na preživljavanje bolesnika na hemodijalizi

## Influence of hemoglobin level and dose of administered recombinant human beta erythropoietin on survival of hemodialysis patients

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**Apstrakt**

**Uvod/Cilj.** Primenom eritropoetina u terminalnom stadijumu hronične bubrežne insuficijencije snižava se kardiovaskularni morbiditet, poboljšava kvalitet života i preživljavanje bolesnika. Cilj ovog ispitivanja bio je da se utvrdi razlika u preživljavanju bolesnika na hemodijalizi koji su lečeni rekombinantnim humanim beta eritropoetinom i bolesnika koji nisu lečeni ovim preparatom, kao i da se ispita uticaj nivoa hemoglobina i doze eritropoetina na preživljavanje bolesnika. **Metode.** Studija je obuhvatila 291 bolesnika, od kojih su 122 bili na terapiji eritropoetinom, a 169 bolesnika činili su kontrolnu grupu. Ispitivanje je sprovedeno u Klinici za nefrologiju i kliničku imunologiju, Kliničkog centra Vojvodine u trajanju od 69 meseci. Analizirani su osnovni demografski parametri, dužina dijaliziranja, osnovna oboljenja, komorbidna stanja, uzroci smrti, parametri krvne slike i doza eritropoetina. Korišćene su statističke metode: deskriptivna analiza, Anova, Manova, diskriminativna analiza, Coxov regresioni model i kriva preživljavanja Kaplan Meier. **Rezultati.** Prosečna starost i dužina dijaliziranja bolesnika u grupi kojoj je primenjen eritropoetin iznosili su 47,88 ± 13,32 godine i 45,76 ± 46,73 meseci, a u kontrolnoj grupi bolesnika 58,73 ± 12,67 godina i 62,80 ± 55,23 meseca. Prosečne vrednosti hemoglobina i hematokrita u grupi koja je primala eritropoetin iznosile su 11,40 ± 8,39 g/dL i 0,35 ± 0,04/L, za razliku od kontrolne grupe bolesnika kod koje su te vrednosti iznosile 8,52 ± 7,73 g/dL i 0,26 ± 0,04/L. Prosečna mesečna doza eritropoetina iznosila je 21 587 ± 10 183,36 IJ/mesečno. Utvrđena je značajna razlika preživljavanja između navedenih grupa bolesnika ($p < 0,05$). Značajnost razlike ($p < 0,05$) utvrđena je kod preživljavanja bolesnika sa primenom eritropoetina u odnosu na nivo hemoglobina (< 100 g/L/100–110 g/L/110–120 g/L/> 120 g/L) i u odnosu na visinu doze eritropoetina (< 20 000 IJ/20 000–40 000 IJ/> 40 000 IJ/mesečno). **Zaključak**. Najbolje preživljavanje imali su bolesnici sa hemoglobinom > 120 g/L i dozom eritropoetina < 20 000 IJ/mesečno.

**Ključne reči:**
**bubreg, hronična insuficijencija; dijaliza; hemoglobini; eritropoetin, rekombinantni; preživljavanje.**

**Abstract**

**Background/Aim.** In patients with end-stage renal disease, treatment with erythropoietin lowers cardiovascular morbidity, improves quality of life and patient survival. The aim of this study was to determine the difference in survival of hemodialysis patients treated with recombinant human beta erythropoietin and patients without this treatment, and to determine the influence of hemoglobin level and erythropoietin dose on the survival of these patients. **Method.** The study included 291 patients undergoing maintenance hemodialysis, 122 were on erythropoietin therapy, 169 patients formed control group. The study was performed at the Clinic for Nephrology and Clinical Immunology, Clinical Center of Vojvodina, during a 69-month period. We analyzed basic demographic parameters, dialysis duration, underlying disease, comorbidities, death causes, bloodwork parameters and erythropoietin dosage. Descriptive statistics, Anova, Manova, discriminant function analysis, Cox regressional model and Kaplan Meier survival curves were used as statistical methods. **Results**. Average age and dialysis duration in the experimental group were 47.88 ± 13.32 years, and 45.76 ± 46.73 months, respectively and in the control group 58.73 ± 12.67 years and 62.80 ± 55.23 months, respectively. Average level of hemoglobin and hematocrit in the group in which erythropoietin had been administered was 11.40 ± 8.39 g/dL and 0.35 ± 0.04/L, while the control group these values were 8.52 ± 7.73 g/dL and 0.26 ± 0.04/L, respectively. Average monthly dosage of erythropoietin was 21 587 ± 10 183.36 IJ/month. Significant difference in survival was determined ($p < 0,05$) between the stated patient groups. A significant difference ($p < 0,05$) was found in survival of the patients in which erythropoietin was administered regarding hemoglobin level (< 100 g/L/100–110 g/L/110–120 g/L/ > 120 g/L), as well as in regard of erythropoietin dose applied (< 20 000 IJ/20 000–40 000 IJ/ > 40 000 IJ/month). **Conclusion**. Best survival was noted in patients with hemoglobin > 120 g/L and erythropoietin dose < 20 000 IJ/month.

**Key words:**
**kidney failure, chronic; dialysis; hemoglobins; erythropoietin, recombinant; survival.**

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## Uvod

Anemija je česta i rana komplikacija hronične bubrežne insuficijencije (HBI) i povezana je sa neželjenim kardiovaskularnim događajima i lošim preživljavanjem bolesnika. Zbog smanjene endogene produkcije eritropoetina, više od 90% bolesnika sa terminalnom HBI zahteva egzogeni eritropoetin ili transfuzije krvi u cilju postizanja i održavanja ciljnih vrednosti hemoglobina (Hgb)[1, 2].

U poslednje dve decenije, primena eritropoetin-stimulišućih agenasa (ESA) zauzima prioritetno mesto u lečenju anemije bolesnika u terminalnom stadijumu HBI. Pokazano je da lečenje anemije primenom ESA poboljšava preživljavanje, snižava kardiovaskularni morbiditet i poboljšava kvalitet života [1, 3–6]. Kada se u korekciji anemije koriste ESA dolazi do regresije hipertrofije leve komore, poboljšanja morfologije leve komore, ejekcione frakcije i kardiovaskularnog statusa [7–9]. U cilju korekcije anemijskog sindroma neophodna je i adekvatna nadoknada parenteralnim preparatima gvožđa. Pollak i sar. [10] ustanovili su da bolesnici na dijalizi sa niskim vrednostima serumskog gvožđa (≤ 5,4 μmol/L), saturacije transferina (≤ 20%) i feritina (≤ 100 μg/L) ređe preživljavaju u poređenju sa bolesnicima koji su lečeni intravenskim preparatom gvožđa [10].

Do sada primenjivani preparati eritropoetina razlikuju se po farmakokinetici i biohemijskom svojstvu, a visoka cena ovih preparata je uticala na njihovu slabiju primenu u našoj zemlji. Efikasnost rekombinantnog humanog beta eritropoetina (rHu-beta-EPO) aplikovanog supkutano u poređenju sa intravenskim davanjem je u dužem poluživotu eliminacije, smanjenju ukupne date doze, učestalosti primene ovog preparata i boljoj kontroli hipertenzije. Međutim, do sada nije formiran određeniji stav u odnosu na način primene zbog mogućih komplikacija i komfornosti ovih bolesnika. Nije jasno definisan ni optimalni nivo hemoglobina za dijalizne bolesnike, s obzirom na moguće konsekvence neadekvatno lečene anemije. Grupe stručnjaka su nakon iscrpnog pregleda aktuelne relevantne literature predložile da se nivo Hgb održava između 11 i 12 g/dL u cilju poboljšanja kvaliteta života, kardiovaskularnog statusa bolesnika i smanjenja broja hospitalizacija [11, 12]. Revidirana preskripcija studija ESA predlaže opseg nivoa Hgb od 10 do 12 g/dL za sve bolesnike [13]. Cilj ovog ispitivanja bio je da se utvrdi razlika u preživljavanju bolesnika na hemodijalizi koji su lečeni primenom rHu-beta EPO i kontrolne grupe bolesnika i ispita uticaj nivoa Hgb i doze rHu-beta EPO na preživljavanje bolesnika.

## Metode

Retrospektivno ispitivanje sprovedeno je na Odeljenju za hemodijalizu Klinike za nefrologiju i kliničku imunologiju Kliničkog centra Vojvodine u periodu od janura 2003. do oktobra 2008. godine. Ispitivanje je obuhvatilo 291 bolesnika starijih od 18 godina. Bolesnici su bili na hroničnom programu hemodijalize tri puta nedeljno po četiri sata; vrsta dijalize bila je bikarbonantna na polisulfonskoj kapilarnoj membrani površine od 1,1–1,3 $m^2$, protoka krvi 250–300 mL/min, vaskularnim pristupom (arterio-venska fistula ili graft fistula i trajni dual lumen kateter). Upotreba rHu-beta EPO započeta je u našem centru početkom 2003. godine kod 37 bolesnika, kada su prioritet pri uključivanju ove terapije imali mlađi bolesnici pripremljeni za transplantaciju bubrega i bolesnici koji su imali reakcije na primenu derivata krvi. Poboljšanim snabdevanjem rHu-beta EPO i broj bolesnika kojima je uključivan ovaj preparat postepeno je bio u porastu narednih godina. Ispitivanje je završeno 30. 09. 2008. godine, jer je od tada većina bolesnika prevedena na druge vrste eritropoetina.

Tokom ispitivanog perioda, anemijski sindrom je kod 122 bolesnika korigovan supkutano aplikovanim rHu-beta EPO i parenteralnim preparatima gvožđa koji su primenjivani prema aktuelnim preporukama internacionalnih vodiča: The National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF-K/DOQI) i (European Best Practice Guidelines) EBPG. Inicijalno, rHu-beta EPO aplikovan je tri puta nedeljno u dozi od 50 do 150 IJ/kg/nedeljno do postizanja ciljnih koncentracija Hgb 11–12 g/dL i Hct 33–36%, uz održavanje postignutih vrednosti (srednja doza održavanja < 125 IJ/kg/nedeljno) individualnim pristupom (smanjenjem ili proređivanjem doze na jednom nedeljno do jednom mesečno). Ova grupa bolesnika bila je podeljena u četiri podgrupe prema nivou pojedinačne prosečne mesečne vrednosti Hgb (< 10 g/dL/10–11 g/dL/11–12 g/dL/ > 12 g/dL), a prema visini pojedinačne prosečne mesečne primenjene doze rHu-beta EPO (< 20 000 IJ/20 000–40 000 IJ/ > 40 000 IJ) u tri podgrupe. Kod 169 bolesnika koji su činili kontrolnu grupu, primenjivana je supstituciona terapija derivatima krvi i preparatima gvožđa. Od intravenskih preparata gvožđa korišćeni su feri-glukonat i dekstriferon. Feri-glukonat je primenjen u dozi od 31,25 do 126 mg, a dekstriferon u dozi od 25 do 150 mg u jednokratnim dozama tri puta nedeljno (6–10 puta na kraju hemodijalize) do postizanja zadovoljavajuće saturacije depoa, kada je nastavljena primena ovih preparata u dozi od 25 do 100 mg (jednom nedeljno).

Parametri krvne slike (eritrociti, Hgb, hematokrit) i doza rHu-beta EPO praćeni su mesečno, a albumini i klirens/volumen distribucije (KT/V) u tromesečnim periodima tokom ispitivanja. Vrednosti serumskog gvožđa, feritina i transferina iz tehničkih razloga nisu praćeni tokom ispitivanja.

Preživljavanje je posmatrano unutar vremenskog perioda od prve hemodijalize do smrtnog ishoda bolesti ili prekida ispitivanja 30. 09. 2008. godine. Bolesnici koji nisu zahtevali hronični hemodijalizni program duže od tri meseca, bolesnici iz drugih hemodijaliznih centara koji su privremeno dijalizirani, oni koji su započeli hemodijalizu u kućnim uslovima, koji su prevedeni sa peritoneumske dijalize na hemodijalizu i transplantirani bolesnici, isključeni su iz statističke analize preživljavanja.

Tokom ispitivanja analizirani parametri bili su: polna i starosna struktura bolesnika, dužina dijaliziranja, osnovna oboljenja kao uzrok terminalne bubrežne insuficijencije, komorbidna stanja, uzroci smrti, parametri krvne slike (eritrociti, Hgb, hematokrit), doza rHu-beta EPO, nutritivni (albumini) i dijalizni parametar (KT/V). Osnovne hematološke analize (Hgb, eritrociti, hematokrit) urađene su na aparatu Beckman Coulter HmX, metodom impendance i protočne citometrije. Referentne vrednosti bile su za Hgb 12–16 g/dL,

eritrocite 3,70–5,80 x $10^{12}$/L i hematokrit 0,35–0,53/L. Albumini su određivani iz seruma ispitanika fotometrijskom metodom na automatizovanom aparatu Olympus AU–400. Referentne vrednosti bile su 33–55 g/L. Uzorci krvi za laboratorijsku analizu uzimani su pre započinjanja dijalize, pre davanja heparina. Adekvatnost hemodijalize procenjivana je na osnovu Kt/Vsp indeksa izračunatog prema sledećoj formuli: $Kt/Vsp = -\ln(C2/C1 - 0.008 \times T) + (4 - 3.5 \times C2/C1) \times UF/W$, gde su: C1 – redijalizna vrednost uree (mmol/L), C2 – postdijalizna vrednost uree (mmol/L), T – trajanje hemodijalize (h), UF – interdijalizni prinos (L), W – telesna masa posle hemodijalize (kg). Prema K/DOQI uputstvima hemodijaliza je adekvatna ukoliko je Kt/V sp, izračunat prema Daugridas formuli druge generacije ≥ 1,2.

Podaci su obrađeni statističkim metodama: deskriptivna analiza, Manova, Anova, diskriminativna analiza, Cox regresioni model i kriva preživljavanja Kaplan Meier. Log-rank test korišćen je u poređenju krivi preživljavanja. Prag značajnosti bio je $p < 0,05$ i $0,10 > p > 0,05$ sa povećanim rizikom zaključivanja.

## Rezultati

U grupi sa primenom rHu-beta EPO bilo je 122 bolesnika, 84 (68,9%) muškaraca i 38 (31,1%) žena, a u grupi bez primene rHu-beta EPO 169 bolesnika, 104 (61,5%) muškaraca i 65 (38,5%) žena.

Učestalost osnovnih oboljenja grupe bolesnika sa rHu-beta EPO bila je sledeća: hipertenzivna nefropatija 36 (29,5%), hronični glomerulonefritis 28 (23,0%), dijabetesna nefropatija 19 (15,6%), policistični bubrezi 14 (11,5%), endemska nefropatija i opstruktivna nefropatija 11 (9,0%) i ostala osnovna oboljenja 3 (2,5%). U kontrolnoj grupi bolesnika učestalost osnovnih oboljenja bila je sledeća: hipertenzivna nefropatija 47 (27,8%), hronični glomerulonefritis 28 (16,6%), dijabetesna nefropatija 25 (14,8%), policistični bubrezi 23 (13,6%), opstruktivna nefropatija 19 (11,2%), endemska nefropatija 16 (9,5%), ostala osnovna oboljenja 11 (6,5%). Utvrđena je značajna razlika ($p < 0,05$) kod opstruktivne nefropatije, policističnih bubrega i ostalih osnovnih oboljenja između ove dve grupe bolesnika.

Starost bolesnika, dužina dijaliziranja, Hgb, hematokrit, albumini i KT/V obe grupe bolesnika prikazani su u tabeli 1. Bolesnici na terapiji rHu-beta EPO bili su značajno mlađi, kraće dužine dijaliziranja, značajno većih vrednosti Hgb, hematokrita, postignute prosečne mesečne doze rHu-beta EPO i vrednosti KT/V u odnosu na kontrolnu grupu bolesnika. Tabela 2 prikazuje numeričke i procentualno izražene vrednosti komorbidnih stanja, a tabela 3 prediktore mortaliteta kod obe grupe bolesnika. Kardiovaskularne bolesti bile su najzastupljenije komorbidno stanje i uzrok smrti kod obe grupe bolesnika. Utvrđena je značajna razlika ($p < 0,05$) komorbiditeta u odnosu na cerebrovaskularne bolesti, hroničnu opstruktivnu bolest pluća i jetrene bolesti između dve grupe bolesnika. Nije ustanovljena značajna razlika ($p = 0,149$) prema uzrocima smrti između grupe bolesnika sa primenom rHu-beta EPO i kontrolne grupe bolesnika.

**Tabela 1**

**Deskriptivna analiza opštih parametara, parametra krvne slike, nutritivnog i dijaliznog parametra ispitanika**

| Parametri praćenja | Grupa sa rHu-beta EPO | Grupa bez rHu-beta EPO | *p* |
|---|---|---|---|
| | $\bar{x} \pm SD$ | $\bar{x} \pm SD$ | |
| Starost (godine) | 47, 88 ± 13,22 | 58,73 ± 12,67 | 0,000 |
| Dužina trajanja hemodijalize (meseci) | 45, 76 ± 46,73 | 62,80 ± 55,23 | 0,005 |
| Hemoglobin (g/dL) | 11, 40 ± 8,39 | 8,52 ± 7,73 | 0,000 |
| Hematokrit (/L) | 0,35 ± 0,04 | 0,26 ± 0,04 | 0,000 |
| Albumini (g/L) | 38,58 ± 1,43 | 37,06 ± 1,36 | 0,716 |
| KT/V - | 1,21 ± 0,18 | 1,15 ± 0,10 | 0,000 |

**rH-beta EPO – rekombinantni humani beta eritropoetin; KT/V – parametar uspešnosti hemodijalize (klirens/volumen distribucije)**

**Tabela 2**

**Brojčana i procentualna zastupljenost komorbidnih stanja kod obe grupe bolesnika**

| Komorbidna stanja na početku dijalize | Grupa bolesnika sa rHu-beta EPO [n(%)] | Grupa bolesnika bez rHu-beta EPO [n(%)] |
|---|---|---|
| Kardiovaskularne bolesti | 50 (41,0) | 65 (38,5) |
| Cerebrovaskularne bolesti | 16 (13,1) | 40 (23,7)* |
| Periferne vaskularne bolesti | 26 (21,3) | 32 (18,9) |
| Dijabetes melitus | 11 (9,0) | 14 (8,3) |
| Ulkusna bolest | 4 (3,3) | 4 (2,4) |
| Maligna bolest | 4 (3,3) | 9 (5,3) |
| Hronična opstruktivna bolest pluća | 9 (7,4) | 5 (3,0)* |
| Bolesti jetre | 2 (1,6) | 0 (0)* |

***$p < 0,05$ i $1,10 > p > 0,05$ sa povećanim rizikom od zaključivanja; rHu-beta EPO – rekombinantni humani beta eritropoetin**

Na slici 1 Kaplan Meier kriva pokazuje značajnu razliku ($p < 0,05$) u mesečnom preživljavanju između obe grupe bolesnika. Tabela 4 prikazuje medijanu preživljavanja u mesecima ukupnog broja bolesnika, bolesnika na terapiji rHu-beta EPO i kontrolne grupe bolesnika. Medijana preživljavanja ukupnog broja bolesnika iznosila je 38,5 meseci, bolesnika koji su lečeni rHu-beta EPO 50,0 meseci, a kontrolne

**Tabela 3**

**Prediktori mortaliteta bolesnika sa i bez primene rHu-beta EPO**

| Komorbidna stanja na početku dijalize | HR | *p* |
|---|---|---|
| Pol | 0,778 | 0,057* |
| Starost | 0,778 | 0,057* |
| Dužina dijaliziranja | 0,152 | 0,036* |
| Osnovna oboljenja | 0,630 | 1,014 |
| Sa rHu-beta EPO/bez rHu-beta EPO | 0,279 | 0,044* |
| Dužina lečenja rHu-beta EPO (meseci) | 0,955 | 0,000* |
| Komorbidna stanja | 0,933 | 0,052* |
| Kardiovaskularne bolesti | 1,162 | 0,842 |
| Cerebrovaskularne bolesti | 0,606 | 0,515 |
| Periferne vaskularne bolesti | 1,025 | 0,974 |
| Dijabetes melitus | 1,421 | 0,656 |
| Ulkusna bolest | 0,921 | 0,923 |
| Maligna bolest | 0,395 | 0,266 |
| Hronična obstruktivna bolest pluća | 0,589 | 0,514 |
| Bolesti jetre | 0,545 | 0,206 |
| Albumini < 33 g/L | 1,006 | 0,015* |
| KT/V | 1,544 | 0,375 |

***p* < 0,05 i 1,10 > *p* > 0,05 sa povećanim rizikom od zaključivanja; HR – *hazard ratio***
**rHu-beta EPO – rekombinantni humani beta eritropoetin; KT/V - klirens/volumen distribucije**

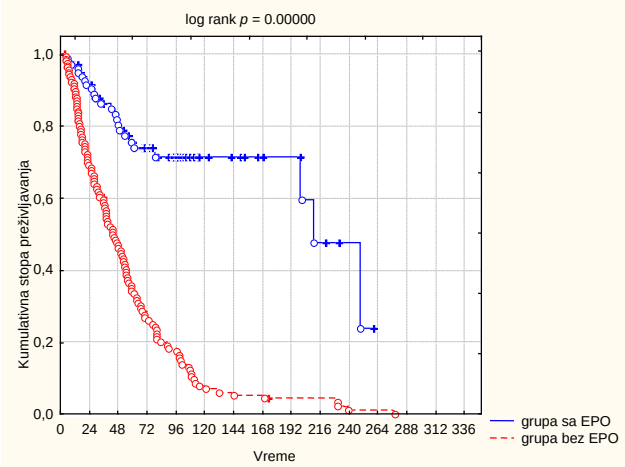
**Tabela 4**

**Preživljavanje bolesnika tokom ispitivanog perioda**

| Grupe bolesnika | Broj bolesnika | Xsr meseci | Medijana (meseci) | min | max | SD |
|---|---|---|---|---|---|---|
| Ukupno bolesnika | 291 | 53,3 | 38,5 | 3,0 | 278 | 50,9 |
| Bolesnici sa rHu-beta EPO | 122 | 45,5 | 38,0 | 6,0 | 249 | 35,6 |
| Bolesnici bez rHu-beta EPO | 169 | 46,2 | 32,0 | 3,0 | 278 | 46,6 |

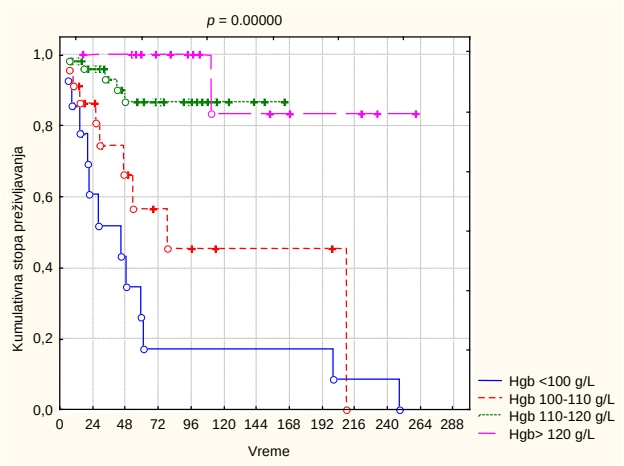
***Xsr – prosečno preživljavanje; rHu-beta EPO – rekombinantni humani beta eritropoetin**

grupe bolesnika 36,5 meseci. Ustanovljena je statistički značajna razlika ($p$ = 0,0069) po medijani preživljavanja grupe bolesnika na terapiji rHu-beta EPO i kontrolne grupe bolesnika.

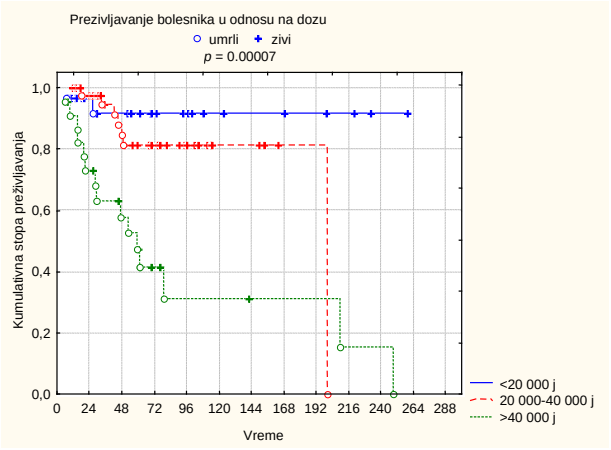



**Sl. 1 – Preživljavanje bolesnika sa i bez primene rekombinantnog humanog beta eritropoetina (rHu-beta EPO) tokom ispitivanog perioda**

Prosečna dužina lečenja rHu-beta EPO iznosila je 34,32 ± 21,04 meseca. U grupi bolesnika sa primenom rHu-beta EPO prosečnu mesečnu dozu < 20 000 IJ imalo je 32 (26,2%) bolesnika, 20 000–40 000 IJ 67 (54,9%) bolesnika i > 40 000 IJ 23 (28,8%) bolesnika. Prosečnu mesečnu vrednost Hgb < 10 g/dL imalo je 14 (11,5%) bolesnika, 10–11g/dL 28 (22,9%) bolesnika, 1–12g/dL 65 (53,3%) bolesnika i > 12g/dL 15 (12,3%) bolesnika. Značajnost razlike ($p$ < 0,05) mesečnog preživljavanja bolesnika lečenih sa rHu-beta EPO u odnosu na nivo vrednosti Hgb (< 10 g/dL/10–11g/dL/11–12 g/dL/ > 12 g/dL) prikazana je Kaplan Meier krivom na slici 2. Na slici 3, Kaplan Meier krivom prikazana je značajna razlika ($p$ < 0,05) mesečnog preživljavanja bolesnika u odnosu na visinu primenjene mesečne doze (< 20 000 IJ/20 000–40 000 IJ/ > 40 000 IJ) rHu-beta EPO.




**Sl. 2 – Preživljavanje bolesnika sa primenom rekombinantnog humanog beta eritropoetina u odnosu nivo hemoglobina (Hgb): < 10 g/dL, 10–11 g/dL, 11–12 g/dL, > 12 g/dL**




**Sl. 3 – Preživljavanje bolesnika u odnosu na visinu primenjene doze rekombinantnog humanog beta eritropoetina (IJ/mesečno): < 20 000 , 20 000–40 000 , > 40 000**

Tokom ispitivanog perioda od 69 meseci, u grupi sa primenom rHu-beta EPO umrlo je 24 (19,7%) bolesnika, dok je u kontrolnoj grupi umrlo 130 (76,9%) bolesnika. Cox regresioni model u tabeli 3 pokazao je značajne faktore rizika od smrtnog ishoda kod obe grupe bolesnika.

## Diskusija

Pored kardiovaskularnih bolesti i sniženih vrednosti Hb, markeri inflamacije, kao što su C-reaktivni protein, oštećena funkcija endotela, malnutricija, kao i nivo parat hormona, poremećen odnos kalcijuma i fosfora, nivo homocisteina, asimetričnog dimetilarginina i dislipidemija povezani su, takođe, sa sniženim preživljavanjem ili sa kardiovaskularnim događajima kod bolesnika sa HBI [14–16].

Utvrđeno je da je Hgb nezavisni pokazatelj kako broja hospitalizacija, tako i preživljavanja bolesnika na hemodijalizi [17]. Na koncentraciju Hgb vremenom utiču prisutna komorbidna stanja, broj hospitalizacija, prethodno primenjene doze eritropoetina i prethodni nivo Hgb [17]. U našem ispitivanju uočeno je da je višegodišnje preživljavanje dijaliznih bolesnika sa primenom rHu-beta EPO bilo značajno veće u odnosu na kontrolnu grupu bolesnika, što je u skladu sa drugim ispitivanjima [18]. Medijana preživljavanja naših bolesnika koji su primali rHu-beta EPO bila je značajno veća (50,0 meseci) u poređenju sa kontrolnom grupom bolesnika (36,5 meseci). Studija u trajanju od devet i po godina uključila je 1 774 bolesnika na hemodijalizi, od kojih je kod 1 731 (97,6%) bolesnika primenjen alfa-eritropoetin, a čija je medijana preživljavanja iznosila 789 dana [10].

Kod naših bolesnika najzastupljeniji komorbiditet bile su kardiovaskularne bolesti, za razliku od studije u kojoj je bio najzastupljeniji komorbiditet dijabetes melitus tipa 2 [10]. Tokom prethodnog ispitivanja u trajanju od 25 meseci kod 30 hemodijaliznih bolesnika na terapiji sa rHu-beta EPO prosečne doze održavanja 3 320,4 IJ/nedeljno postignuta je parcijalna regresija hipertrofije leve komore smanjenjem indeksa mase leve komore za 17,86% [19]. Kardiovaskularne bolesti bile su i vodeći uzrok smrti kod naših bolesnika, što odgovara rezultatima dosadašnjiih studija [20]. U jednoj studiji najveći procenat svih uzroka smrti i kardiovaskularnih uzroka smrti imali su bolesnici sa dozom ≥ 18 000 IJ/nedeljno i najnižom postignutom ciljnom vrednošću Hgb [18].

Postoje podaci koji ukazuju da je nivo Hgb direktno i indirektno povezan sa preživljavajem bolesnika sa HBI, ali je većina ovih podataka prikupljena od bolesnika u terminalnom stadijumu HBI [4]. Kod bolesnika na hemodijalizi pokazano je da su perzistentno i tranzitorno nizak nivo Hgb i velike varijacije nivoa Hgb povezani sa porastom rizika od smrtnog ishoda bolesti, dok, nasuprot tome, tranzitorno i perzistentno visok nivo Hb nije povezan sa porastom rizika od smrtnog ishoda bolesti [21]. S obzirom na to da još uvek nisu precizno definisane ciljne vrednosti Hgb, dosadašnji rezultati povezanosti nivoa Hgb i preživljavanja bolesnika na hemodijalizi su različiti.

Mnoge studije ukazale su na veći morbiditet i mortalitet onih bolesnika kod kojih je ciljna vrednost serumskog Hgb identična nivou u opštoj populaciji [22–24]. Vrednosti Hgb 12–13 g/dL povezane su sa manjim rizikom od smrtnog ishoda bolesti, dok su vrednosti Hgb 11–11,5 g/dL, koje su najniže preporučene vrednosti prema K/DOQI uputstvu, povezane sa višim rizikom smrtnosti ovih bolesnika [25]. Vrednosti Hgb > 13,5 g/dL takođe su povezane sa višim rizikom od smrtnosti, ali se ne razlikuje značajno od rizika kod bolesnika sa Hgb 11–11,5 g/dL [18]. Robinson i sar. [26] ustanovili su da je nivo Hgb ≥ 11 g/dL povezan sa dužim preživljavanjem bolesnika na hemodijalizi, dok za bolesnike čije su vrednosti bile ≥ 12 g/dL, ova veza nije utvrđena. U ovoj studiji je i utvrđeno da je nivo Hgb < 11 g/dL pokazatelj povećanog rizika mortaliteta kod svih bolesnika na hemodijalizi, a ne samo kod onih sa komplikacijama osnovne bolesti ili komorbidnim stanjima [26].

U našoj studiji, u grupi bolesnika sa primenom rHu-beta EPO, najbolje preživljavanje su imali bolesnici sa Hgb > 12 g/dL što odgovara dosadašnjim rezultatima studija, u poređenju sa bolesnicima sa nižom vrednostima Hgb (11–12 g/dL, 10–11 g/dL, < 10 g/dL) [10, 26, 27]. U odnosu na visinu doze rHu-beta EPO, najčešće su preživljavali bolesnici sa prosečnom mesečnom dozom < 20 000 IJ, u poređenju sa dozama 20 000–40 000 IJ i > 40 000 IJ. Regidor i sar. [18] utvrdili su veći rizik smrtnog ishoda bolesti kod onih bolesnika koji su zahtevali doze ≥ 18 000 IJ/nedeljno ESA [18]. Skoro objavljena sekundarna analiza CHOIR (*Correction of Hemoglobin and Outcomes in Renal Insufficiency)* studije ukazuje da su visoke doze epoetina alfa, a ne visoke vrednosti Hgb odgovornije za lošiji ishod bolesti [28]. U skorašnjoj studiji ustanovljeno je da je uticaj alfa eritropoetina na preživljavanje bolesnika veoma mali, ali da su najbolje preživljavali bolesnici sa dozom ESA ≤ 12 100 IJ/nedeljno [10]. Najćešći uzroci neadekvatnog odgovora na rHu-beta EPO su apsolutni ili relativni deficit gvožđa, inflamatorna stanja, hronični gubici krvi, malnutricija i nedovoljna doza dijalize. Stoga, multifaktorskom Cox regresionom analizom ustanovili smo da su starost, pol, dužina dijaliziranja, odsustvo terapije eritropoetinom, dužina lečenja eritropoetinom u mesecima, komorbidna stanja i hipoalbuminemija značajno uticali na preživljavanje bolesnika. Parametar uspešnosti hemodijalize KT/V nije

značajno uticao na preživljavanje bolesnika lečenih redovnim hemodijalizama. Selim i sar. [29] ustanovili su da vrednost albumina < 35 g/L značajno utiče na preživljavanje bolesnika na dijalizi [29]. U skorašnjoj studiji utvrđeno je da vrednost albumina > 40 g/L i KT/V > 1,6 značajno utiču na preživljavanje ovih bolesnika [10].

Ovom studijom nisu bili obuhvaćeni parametri zasićenja gvožđa, inflamacije, lipidnog i koštanog statusa od kojih, takođe, zavisi stepen korekcije anemije kao odgovor na terapiju ESA. Kod naših bolesnika nije bio ni zanemarljiv procenat zastupljenosti inflamatornih bolesti kao uzroka smrti, a s obzirom na postojanje više vrsta vaskularnih pristupa, nije ispitivan rizik od infekcije, inflamacija i prisustva tromboziranih arteriovenskih pristupa koji bi, takođe, mogli biti uzrok neadekvatnog odgovora na ESA. U nekom od narednih ispitivanja trebalo bi analizirati prethodno navedene parametre.

## Zaključak

Rezultati ovog ispitivanja pokazali su da su najbolje preživljavanje imali bolesnici sa nivom Hgb > 120/dL i dozom rHu-beta EPO < 20 000 IJ/mesečno. Potrebna su dalja ispitivanja povezanosti anemije, lečenja anemije i preživljavanja.

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Primljen 26. I 2010.
Revidiran 23. VI 2010.
Prihvaćen 3. VIII 2010.

ORIGINAL ARTICLE

UDC:616.379-008.64:616-002
DOI:10.2298/VSP1109756M

# Influence of glucoregulation quality on C-reactive protein, interleukin-6 and tumor necrosis factor-α level in patients with diabetes type 1

## Uticaj kvaliteta glikoregulacije na nivo C-reaktivnog proteina, interleukina-6 i tumor nekrozis faktora-α kod bolesnika sa dijabetesom tipa 1

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**Abstract**

**Background/Aim.** Results of studies which have proved an increased inflammatory activity in diabetes type 1, have been published over recent years. One of possible mechanisms that are used to explain chronic inflammation in diabetes is the state of hyperglycemia leading to the enhanced synthesis of glycosylation end products (AGEs) which activate macrophages, increase the oxidative stress and affect the synthesis of interleukins (IL-1, IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP). The aim of the study was to determine the inflammatory markers (CRP, IL-6, TNF-α) in patients with diabetes type 1 and to establish their correlation with glucoregulation parameters and other cardiovascular risk factors as well as to compare them with the healthy controls. **Methods.** The study included 76 patients with diabetes type 1 and 30 healthy controls. We determined values of inflammatory markers (CRP, IL-6, TNF-α) and glucoregulation parameters (fasting glucose $HbA_{1c}$). **Results.** The values of CRP ($p = 0.014$), IL-6 ($p = 0.020$) and TNF-α ($p = 0.037$) were statistically significantly higher in the diabetic patients than in the healthy controls. There was a positive correlation between CRP with postprandial glycemia ($p = 0.004$); the multivariate regression analysis revealed a statistically significant correlation between CRP and age ($p = 0.001$), smoking ($p = 0.055$), fasting glucose ($p = 0.021$) and triglycerides ($p = 0.048$) as well as between IL-6 and LDL-cholesterol ($p = 0,009$). No statistically significant correlations were found between glycosilated hemoglobin ($HbA_{1c}$) and the inflammatory markers (CRP, IL-6 and TNF-α). **Conclusion.** The patients with type 1 diabetes were found to have a low level of inflammatory activity manifested by the increased values of CRP, IL-6 and TNF-α.

**Key words:**
**diabetes mellitus, type 1; blood glucose; c-reactive protein; interleukin-6; tumor necrosis factor-alpha; sensitivity and specificity.**

Apstrakt

**Uvod/Cilj.** Poslednjih godina objavljeni su rezultati studija koje su dokazale da i kod dijabetesa tipa 1 postoji povećana inflamatorna aktivnost. Jedan od mogućih mehanizama kojima se pokušava objasniti hronična inflamacija kod dijabetesa je stanje hiperglikemije s posledičnim povećanjem sinteze krajnjih produkata glikozilacije (AGE), koji aktiviraju makrofage, povećavaju oksidativni stres i utiču na sintezu interleukina (IL-1, IL-6), tumor nekrozis faktora-α (TNF-alfa) i C-reaktivnog proteina (CRP). Cilj rada bio je određivanje inflamatornih markera (CRP, IL-6, TNF-alfa) kod bolesnika sa dijabetesom tipa 1, te utvrđivanje njihove povezanosti sa parametrima glikoregulacije i drugim kardiovaskularnim faktorima rizika, kao i njihovo poređenje sa vrednostima kontrolne grupe zdravih ispitanika. **Metode.** Ispitivanje je sprovedeno kao unakrsna studija preseka na 76 bolesnika sa dijabetesom tipa 1, dok je kontrolnu grupu činilo 30 zdravih ispitanika. Određivani su markeri inflamacije (CRP, IL-6, TNF-alfa) i parametri glikoregulacije (glikemija, $HbA_{1c}$). **Rezultati.** Vrednosti CRP ($p = 0,014$), IL-6 ($p = 0,020$), TNF-α (v 0,037) bile su statistički značajno više u grupi dijabetesnih bolesnika nego u kontrolnoj grupi zdravih osoba. Utvrđeno je postojanje statistički značajne pozitivne korelacije CRP sa glikemijom postprandijalno ($p = 0,004$), dok je primenom multivarijantne regresione analize nađena statistički značajna korelacija CRP sa godinama života ($p = 0,001$), pušenjem ($p = 0,055$), glikemijom našte ($p = 0,021$) i trigliceridima ($p = 0,048$), a istom metodom i statistički značajna korelacija IL-6 sa LDL-holesterolom ($p = 0,009$). Nisu nadjene statistički značajne korelacije između HbA1c i inflamatornih markera CRP, IL-6 i TNF-α. **Zaključak.** Kod bolesnika sa dijabetesom tipa 1, u odnosu na zdrave ispitanike, postoji inflamatorna aktivnost niskog stepena koja se ogleda kroz povišene vrednosti CRP, TNF-alfa i IL-6. Od parametara glikoregulacije izdvojile su se glikemija našte i postprandijalno koje pozitivno korelišu sa vrednostima CRP, dok nisu nađene statistički značajne korelacije sa HbA1c.

**Ključne reči:**
**dijabetes melitus, insulin-zavisni; glikemija; c-reaktivni protein; interleukin-6; faktor nekroze tumora; osetljivost i specifičnost.**

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## Introduction

Numerous epidemiological and clinical studies as well as those performed on autopsy material have proved that atherogenesis develops earlier in patients with diabetes type 1 than in healthy population, thus making the progression of cardiovascular complications far more expressed [1, 2]. It is perfectly clear that atherogenesis is a chronic inflammatory process and this fact has been corroborated by results of numerous studies which have found increased values of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). Many studies, whose results have been published in recent years, have shown that diabetes type 1 is also associated with the increased inflammation [2]. One of the mechanisms which might explain chronic inflammation in diabetes is the condition of hyperglycemia, which leads to an increased synthesis of advanced glycation endproducts (AGEs) resulting from the interaction of glucose in high concentrations with structural and circulating proteins. Advanced glycation end products are considered to activate macrophages, increase the oxidative stress and affect the synthesis of IL-1, IL-6, TNF-α and CRP. Of all the proteins of the acute phase and plasma inflammatory markers, C-reactive protein (CRP) has been most widely studied and it is believed to have a very important role in the endothelial dysfunction and the process of atherosclerosis. It is also considered to be one of the important and independent predictors of future cardiovascular events. Hepatocytes produce CPR as a response to the increased level of IL-6, IL-1, TNF-α [1–3], which is a sensitive infection marker and it is produced as a systemic inflammatory response to a local or systemic infection. It is widely used in clinical setting to follow not only the disease course but also the effects of the applied antiinflammatory and antibiotic therapy [3, 4]. A high sensitivity C-reactive protein is used to detect small changes of CRP levels associated with an increased cardiovascular risk in healthy population [5]. Interleukin 6 is an intercellular mediator and primary indicator of the liver CPR [6]. Although it originates from T cells, other cells such as macrophages, monocytes, smooth-muscle cells, epithelial/endothelial/mesangial cells, fibroblasts, synovial cells, osteoblasts as well as chondrocytes may also be provoked to produce IL-6 [7]. An increased IL level is present in many autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus as well as in diabetes of both types 1 and 2 [8–10]. The circulating IL-6 stimulates hypothalamic-hypophyseal axis whose activation is responsible for the central obesity, hypertension and insulin resistance [11, 12]. TNF-α is a pleiotropic cytokine produced by various cells such as macrophages, endothelial and smooth-muscle cells. It is one of the most important cytokines in the intercellular communication [13]. Recent studies have proved that TNF-α activation may directly or indirectly affect pathogenesis and induce macrovascular complications in diabetes as well as atherosclerotic vascular lesions [14, 15]. It has a major role in the amplification of inflammatory cascade. TNF-α also plays a certain role in damaging the pancreas beta cells by being responsible not only for diabetes type 1 pathogenesis but for the development of insulin resistance associated with obesity and diabetes type 2, as well [15, 16].

The aim of the study was to analyse the level of inflammatory markers CRP, IL-6 and TNF-α in a group of patients with diabetes type 1 and a group of healthy controls and to correlate their values with the parameters of glycoregulation such as glycosylated hemoglobin ($HbA_{1c}$), fasting and postprandial glycemia as well as lipid and lipoprotein status.

## Methods

This cross-sectional study was performed on a group of 106 subjects, of whom 76 were the patients with diabetes type 1 and 30 were the healthy controls. The study group consisted of the patients with diabetes type 1, which had been diagnosed before they were 36 years of age and who were on insulin therapy in the first year after the diagnosis had been made. They either visited day hospital for diabetes or were hospitalized in the Department of Endocrinology, Clinical Center of Vojvodina. The group of healthy controls consisted of 30 subjects of both sexes, of approximately the same age, normally nourished and without other risk factors for atherosclerosis.

The following data were taken for both groups of subjects: sex, age, length of the disease, age when the disease was diagnosed, smoking habit and family medical history. To assess the state of metabolic regulation in diabetes the values of fasting glycemia were taken 2 hours after breakfast as well as the values of HbA1c; when the latter were less than 7.5% they pointed to the satisfactory glucoregulation in diabetes, whereas when they were over 7.5%, glucoregulation was considered unsatisfactory. Values of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were measured to analyze the lipid and lipoprotein status. The nourishment status was assessed on the basis of anthropometric measurements, body mass, body height and body mass index (BMI). The waist was measured in centimeters and the recommended values according to the IDF criteria [17] were considered to be desirable: less than 80 cm for women and less than 94 cm for men. The following inflammatory markers were determined: serum fibrinogen concentrations, CRP, IL-6 and TNF-α. The serum samples were kept at -80ºC before being analyzed. C-reactive protein was determined by electrochemiluminescence, and the referral values were from 0 to 5mg/L. TNF-α and IL-6 were determined in the Laboratory for Immunology, Department of Nephrology and Immunology, Clinical Center Vojvodina by commercial ELISA plates according to the standard procedure recommended by the manufacturer.

The collected data were processed by the methods of descriptive and inferential statistics. The following was presented as the numerical characteristics: the arithmetic mean, median, standard deviation and either the value range or the interquartile range, depending on the data nature. Mean values of the numerical characteristics of the two groups were compared by the *t*-test. Differences in the distribution of numerical non-homogenous characteristics between the two

groups were compared by the nonparametric Mann-Whitney test and among three groups by the Kruskal-Wallis test. The correlation of the two characteristics were examined by the Spearman's coefficient of correlation. Multivariate regression analysis was applied to determine the predictions and correlations between dependent variables with independent ones: the linear regression was used when the dependent variable was continuous and the logistic regression model was applied when the dependent variable was dichotomous (binary).

## Results

Table 1 shows the characteristics of the study and the control group which did not differ in sex and age structure, nourishment status, values of total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides. Not surprisingly, the study group had statistically significantly higher values of fasting glycemia ($p = 0.000$), postprandial glycemia ($p = 0.003$) as well as the values of HbA1c ($p = 0.000$) compared to the healthy controls. The values of CPR ($p = 0.014$), IL-6 ($p = 0.0200$), TNF ($p = 0.037$) were statistically significantly higher in the diabetic patients than in the healthy controls. The average duration of diabetes in the group of diabetic patients was 20.01 years.

As shown in Table 2, the correlation between CRP and postprandial glycemia was significant ($p = 0.021$) and positive. No significant correlation was found between fasting glycemia and CRP, TNF-α, IL-6 nor between postprandial glycemia and TNF-α and IL-6.

According to the $HbA_{1c}$ value, which was over 7.5% in almost 87% of the patients (Table 3) it was concluded that the study group of the diabetic patients had a poor metabolic regulation. No statistically significant correlation was found between $HbA_{1c}$ and CRP ($p = 0.878$), IL-6 ($p = 0.249$) and TNF-α ($p = 0.817$).

When multiple linear regression was applied, the CRP value was regarded as a dependent variable, and the rest of the mentioned values were regarded as independent variables. The following variables were found to be significant CRP predictors: age, smoking habit, fasting glycemia, triglycerides; whereas sex, age, LDL-cholesterol and triglycerides were significant for predicting IL-6 levels. All independent variables shown in Table 4 (the reduced model) were significantly correlated with the CRP value ($F = 6.568$, $p = 0.000$) and IL-6 value ($F = 3.121$, $p = 0.020$).

**Table 1**

**Characteristics of the study and the control group**

| Patients characteristics and parameters | Study group (n = 76) | Control group (n = 30) | *p* |
|---|---|---|---|
| Sex (male/female) | 32/44 | 12/18 | 0.899 |
| Age (years) | 35.24 ± 11.09 | 38.10 ± 12.97 | 0.454 |
| BMI (kg/m$^2$) | 23.67 ± 3.13 | 23.88 ± 2.49 | 0.843 |
| Waist (desirable/risky) | 60/16 | 18/12 | 0.182 |
| Duration of DM (years) | 20,01± 8,78 | / | |
| Fasting glycemia (mmol/L) | 10.84 ± 4.84 | 4.87 ± 0.78 | 0.000 |
| Postprandial glycemia (mmol/L) | 11.30 ± 5.34 | 6.09 ± 0.47 | 0.003 |
| HbA1c (%) | 9.20 ± 1.71 | 5.55 ± 0.19 | 0.000 |
| Total cholesterol (mmol/L) | 5.22 ± 1.02 | 5.00 ± 0.38 | 0.488 |
| HDL-cholesterol (mmol/L) | 1.39 ± 0.35 | 1.39 ± 0.25 | 0.978 |
| LDL-cholesterol (mmol/L) | 3.27 ± 0.86 | 3.16 ± 0.26 | 0.675 |
| Triglycerides (mmol/L) | 0.92 (0.69–1.49) | 0.92 (0.64–1.24) | 0.716 |
| CRP (mg/L) | 1.20 (0.70–2.78) | 0.50 (0.10–1.40) | 0.014 |
| IL-6 (pg/mL) | 0.76 (0.35–1.25) | 0.15 (0.00–0.91) | 0.020 |
| TNF-α (pg/mL) | 0.65 (0.22–1.70) | 0.20 (0.00–0.45) | 0.037 |

**Data in Table 1 are shown as absolute numbers (the significance for $\chi^2$ test) or $\bar{x} \pm SD$ (the significance for *t*-test). Median (interquartile range) is given for triglycerides, inflammatory markers CRP, IL-6, TNF-α; the significance being for Mann-Whitney test**
**BMI – body mass index; $HbA_{1c}$ – glycosilated hemoglobin; CRP – C-reactive protein; IL-6 – interleukin-6; TNF-α – tumor necrosis factor α**

**Table 2**

**Correlation between the inflammatory marker values and fasting and postprandial glycemia (pp)**

| Markers | Coefficient glycemia | | Significance glycemia | |
|---|---|---|---|---|
| | (fasting) | (pp) | (fasting) | (pp) |
| CRP (mg/L) | 0.131 | 0.265 | 0.261 | 0,021 |
| IL-6 (pg/mL) | 0.009 | 0.052 | 0.941 | 0.655 |
| TNF-α (pg/mL) | 0.176 | 0.206 | 0.131 | 0.076 |

**CRP – C-reactive protein; IL-6 – interleukin-6; TNF-α – tumor necrosis factor α**

**Table 3**

**Correlation between CRP, IL-6, TNF-α and HbA1c**

| $HbA_1$c (normal/increased) | n | Mean value | Median | SD | *p* |
|---|---|---|---|---|---|
| CRP (mg/L) | 10/66 | 2.01/2.26 | 1.25/1.20 | 2.04/2.75 | 0.878 |
| IL- 6 (pg/mL) | 10/66 | 0.74/1.28 | 0.50/0.79 | 0.70/1.55 | 0.249 |
| TNF- α (pg/mL) | 10/66 | 1.19/1.41 | 0.43/0.70 | 1.52/2.46 | 0.817 |

**HbA1c – glycosilated hemoglobin; CRP – C-reactive protein; IL-6 – interleukin-6; TNF-α – tumor necrosis factor α**

**Table 4**

**Linear regression model with dependent variables IL-6 and CRP**

| Independent variables | Reduced model for IL-6 | | | Reduced model for CRP | | |
|---|---|---|---|---|---|---|
| | Coefficient | *t* | *p* | Coefficient | *t* | *p* |
| Sex | -0.207 | -1.698 | 0.094 | | | |
| Age | -0.010 | -1.971 | 0.053 | 0.018 | 3.343 | 0.001 |
| Duration of diabetes | | | | | | |
| Before/after puberty | | | | | | |
| Smoking habit | | | | 0.248 | 1.955 | 0.055 |
| BMI | | | | | | |
| Waist | | | | | | |
| Fasting glycemia | | | | 0.039 | 2.950 | 0.004 |
| Postprandial glycemia | | | | | | |
| HbA1c | | | | | | |
| LDL-cholesterol | 0.176 | 2.680 | 0.009 | | | |
| HDL-cholesterol | | | | | | |
| Triglycerides | -0.141 | -1.869 | 0.066 | 0.163 | 2.008 | 0.048 |
| $R^2$ | 15% | | | 31,9% | | |

**IL-6 – interleukin-6; CRP – C-reactive protein; BMI – body mass index; HbA1c – glycosilated hemoglobin**

According to the obtained coefficient value it can be stated that 31.9% of the changes were in the CRP level; 15% of the changes in the values of IL-6 were explained by the changes in values of independent variables from Table 4 (the reduced model).

## Discussion

Inflammation and oxidative stress play an important role in the process of atherosclerosis; therefore, patients having diabetes type 1 are at higher risk for cardiovascular morbidity and mortality. Although the majority of studies on these problems dealt with diabetes type 2, recently published results have indicated that there is an increased inflammatory activity in patients having diabetes type 1, as well [1, 2, 7, 11, 13, 15]. The afore mentioned has been corroborated by our results as well, which have shown that patients with diabetes type 1 have a low degree of an inflammatory activity, which is reflected through the increased values of CRP, TNF-α, IL-6. All of the studied inflammatory markers, CRP, IL-6, TNF-α were significantly higher in the diabetic patients than in the healthy controls. These results are in accordance with the results of studies which have found increased CRP in adults having diabetes type 1 [11, 12]. Although the mechanism of CRP rise is not completely clear, it seems to be associated with the activation of macrophages, increased oxidative stress and induction of cytokines. In their study, Okano et al. [18] observed statistically significantly higher CRP values in patients with diabetes type 1 than in the healthy controls. Their study did not show statistically significant differences in age, the nourishment status index, values of LDL-cholesterol, HDL-cholesterol and triglycerides between the diabetic patients and healthy controls. This study has clearly shown that the increased level of hs-CRP correlated with the early stage of carotid atherosclerosis in young patients having diabetes type 1, measured through the level of carotid intima-media thickness [18]. Alexandraki et al. [19] found higher values of CRP, IL-6 and TNF-α in the patients with diabetes type 1 than in the healthy controls. However, the values of the above mentioned inflammatory markers were lower than in the group of patients having diabetes type 2.

Chronic hyperglycemia results in advanced glycation end products (AGE), which activate macrophage, increase the oxidative stress and affect the synthesis of IL-6, IL-1, TNF-α and CRP. A great number of studies has clearly shown a significant correlation between HbA1c, fasting and postprandial glycemia and the inflammatory markers CRP, IL-6 and TNF-α [19–25]. A positive correlation was found between the values of CRP and postprandial glycemia and the one with fasting glycemia was determined by the multivariate regression analysis. These results are in accordance with the most recent opinions about the importance of postprandial hyperglycemia in the development of inflammation and chronic complications. Postprandial hyperglycemia is a very frequent phenomenon in patients with both type 1 and type 2 diabetes, and it can be also found in patients with well-regulated diabetes, assessed on the basis of HbA1c values [18–20]. Postprandial hyperglycemia increases the oxidative stress and together with hypertriglyceridemia increases the production of intercellular adhesion molecules (ICAM) and vascular cell adhesion molecules (VCAM), E-selectin as a marker of the endothelial dysfunction, thus affecting the increased production of inflammatory cytokines [22–25]. Our results did not show a significant correlation between the inflammatory markers (CRP, IL-6, TNF-α) and the values of $HbA_{1c}$. Such findings may be explained by the fact that almost 87% of the patients were metabolically unregulated, two fifth of them having $HbA_{1c}$ values over 9.5%. These results can be compared with the results of some studies which have also failed to show the existence of a significant correlation between inflammatory markers and $HbA_{1c}$ [10, 20], thus making it clear that factors other than hyperglycemia affect inflammation and endothelial dysfunction in diabetes.

Dyslipidemia in diabetes type 1 is mostly the result of a poor metabolic regulation of the diseases, with the consequent increase in triglycerides and decrease in HDL-cholesterol [26]. Besides, the development and progression of nephropathy in diabetes type 1 contribute to the development of dyslipidemia together with the increase in the total cholesterol, LDL-cholesterol, total triglycerides and the decrease in the protective HDL2-cholesterol [26, 27]. At the same time,

hyperlipoproteinemia, and particularly hypercholesterolemia, can be an important risk factor for the progression of diabetic nephropathy, as it has been proved in many studies on patients with diabetes type 1 [28–30]. No statistically significant differences in the values of total cholesterol, HDL cholesterol and triglycerides were found between the study group of diabetic patients and the healthy controls. Such results are in accordance with the studies which failed to prove the existence of statistically significant differences in the values of lipid parameters between the healthy subjects and the patients with diabetes type 1 [31–33].

A statistically significant correlation between CRP and triglycerides as well as between IL-6 with triglycerides and LDL-cholesterol was found by the multivariate regression analysis. The same analysis failed to find any correlations between TNF-α and inflammatory markers. Eurodiab study [34] has clearly shown a correlation between the values of triglycerides and HDL cholesterol with inflammatory markers, and it has been confirmed in the healthy population, as well. They have not confirmed a statistically significant correlation between LDL and inflammatory markers [34, 35]. In their study, Ladeia et al. [36] found a significant correlation between CRP and the values of triglycerides and the ratio of triglycerides/HDL. The study did not show a correlation of CRP and other lipid parameters. Increased values of TNF-α in patients with diabetes type 1 and its role as an inflammatory cytokine in the pathogenesis of diabetic nephropathy and other micro- and macrovascular complications have been confirmed by numerous studies [36–38]. Our study also confirmed increased values of TNF-α in the diabetic patients. However, no correlation was found between TNF-α and lipid and lipoprotein parameters, that being in accordance with the results of some other authors [39, 40].

**Conclusion**

In the patients with diabetes type 1 there is a low degree of an inflammatory activity which is manifestated by higher values of CRP, TNF-α and IL-6 compared to the healthy controls. Future prospective studies should prove the importance of inflammation in the pathogenesis of chronic micro- and macrovascular complications in the population of diabetic patients, as well.

Correlations of certain inflammatory markers with glucoregulation parameters, lipid parameters and hypertension offer the possibility of therapeutic modification of inflammation in diabetes indirectly by improving glucoregulation, treating dyslipidemias and hypertension.

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Received on January 28, 2010.
Revised on September 22, 2010.
Accepted on October 1, 2010.

ORIGINAL ARTICLE

UDC: 616-073.75:537.635]:616.728.3-001
DOI:10.2298/VSP1109762J

# Bone bruise of the knee associated with the lesions of anterior cruciate ligament and menisci on magnetic resonance imaging

## Koštana modrica na kolenu udružena sa lezijama prednje ukrštene veze i meniskusa na snimku magnetnom rezonancom

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**Abstract**

**Background/Aim.** Bone bruise is a common finding in acutely injured knee examined by magnetic resonance (MR). The aim of the study was to determine the association of bone bruise frequency with postinjury lesions of anterior cruciate ligament (ACL) and menisci. Bone bruise involves posttraumatic bone marrow change with hemorrhages, edema and microtrabecular fractures without disruption of adjacent cortices or articular cartilage. MR imaging is a method of choice for detecting bone bruises which can not be seen on conventional radiographic techniques. **Methods.** A representative review of 120 MR examinations for the acute knee trauma was conducted. All the patients were examined within one month of trauma. All MR examinations were performed by using a 0.3T MR unit. **Results**. Posttraumatic bone bruise was seen in 39 (32.5%) patients out of 120. Three patients had fracture of the cortex, so-called "occult" fracture (not seen on plain radiography). We analyzed only bone bruises without these fractures of the cortex. Bone bruise was associated with the lesion of ACL in 27 (69%) patients. In 28 (72%) patients bone bruise was in combination with the lesion of menisci. Only two patients with bone bruise had neither ACL nor menisci lesions. There were 78 patients without bone bruise but 33 (43%) of them had lesions of ACL and 49 (63%) had lesions of menisci. **Conclusion.** Bone bruise is best seen in STIR (Short TI Inversion Recovery) images and is very often found in acute knee trauma. Very often it is associated with posttraumatic lesions of ACL and menisci, so attention must be paid to this when bone bruise is seen. The difference in frequency of internal structures of the knee lesions in patients with bone bruise is highly statistically significant as compared to patients with no bone bruise.

**Key words:**
**knee injuries; bone and bones; contusions; magnetic resonance imaging; sensitivity and specificity.**

**Apstrakt**

**Uvod/Cilj.** Koštana modrica predstavlja uobičajen nalaz kod akutne povrede kolena na magnetnoj rezonanci (MR). Cilj rada bio je da se proceni stepen udruženosti koštane modrice (KM) sa posttraumatskim lezijama prednje ukrštene veze (*ligamentum cruciatum anterior* – LCA) i meniskusa. Koštana modrica je posttraumatska promena koštane srži koja je posledica kombinacije hemoragije, edema i mikrotrabekularne frakture bez prekida kontinuiteta korteksa. Magnetna rezonanca je metoda izbora za prikazivanje koštanih modrica koje se ostalim radiološkim metodama ne mogu prikazati. **Metode.** Magnetnom rezonancom pregledano je 120 bolesnika sa akutnom traumom kolena. Svi bolesnici pregledani su u prvih mesec dana nakon traume. Pregledi su obavljeni na 0,3T MR aparatu. **Rezultati.** Posttraumatska KM viđena je kod 39 (32,5%) bolesnika od ukupno 120. Kod tri bolesnika uočeno je prisustvo i frakture korteksa, takozvana okultna fraktura koja nije uočena na radiografiji. Analizirali smo samo čiste koštane modrice bez frakture korteksa. Nalaz KM bio je u kombinaciji sa lezijom LCA kod 27 (69%) bolesnika. Kod 28 (72%) bolesnika KM je bila u kombinaciji sa lezijom meniskusa. Kod dva bolesnika nalaz KM bio je bez patološkog nalaza na LCA i meniskusima. Bez KM bilo je 78 bolesnika, ali njih 33 (43%) imalo je lezije LCA, a 49 (63%) lezije meniskusa. **Zaključak.** Koštana modrica najbolje se uočava u *Short TI Inversion Recovery* (STIR) sekvenci i čest je nalaz kod akutne traume kolena. Veoma često je udružena sa posttraumatskim lezijama LCA i meniskusa, pa na njih posebno treba obratiti pažnju pri pregledu sa nalazom KM kolena. Razlika učestalosti lezija untrašnjih struktura kolena kod bolesnika sa nalazom KM je statistički visokoznačajna u odnosu na bolesnike bez nalaza KM.

**Ključne reči:**
**koleno, povrede; kost; kontuzije; magnetna rezonanca, snimanje; osetljivost i specifičnost.**

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## Introduction

Bone bruise is a common finding in acutely injured knee examined by magnetic resonance (MR). Bone bruise is posttraumatic bone marrow change which is caused by the combination of hemorrhage, edema and microtrabecular fracture without disruption of adjacent cortex. Magnetic resonance imaging is a method of choice for detecting bone bruises which usually can not be seen using other radiological methods [1]. The terms: bone bruise, bone contusion and posttraumatic edema of the bone marrow have been seen for the last ten years in scientific literature and are in fact synonyms in the case of posttraumatic findings of bone marrow contusion. It must be emphasized however that edema of the bone marrow is not specific and that it can be present not only in trauma but also in infection, ischemia, migratory osteoporosis, early osteonecrosis, as a reaction to a neoplasm or even it can be idiopathic [2–5]. Sensitivity of MR imaging for detecting bone bruise of the knee is 83%–96% and specificity is 86%–96% [6]. Bone bruise of the knee is very important as a reason for acute pain and reduced knee function in patients [7, 8]. Precise analysis of bone bruise location can explain the injury pattern which enables better insight in associated lesions of the internal knee structures [9–11]. Magnetic resonance findings show decreased signal intensity in T1 sequence, increased in T2 sequence and hyperintensity of the signal in STIR (Short T1 Inversion Recovery) sequence. Bone bruise is best seen in STIR sequence. The aim of this study was to evaluate the diagnostic power of MR in detecting bone bruise of the knee and to show the association anterior cruciate ligament (ACL) and menisci lesions with bone bruise of the knee.

## Methods

Magnetic resonance imaging of the knee was performed in 120 patients with the acute trauma. All the patients were examined within one month of the trauma. There were 88 (73%) male patients and 32 (27%) women, average age 31 years. All scans were performed by using 0.3T MR with SE T1W1, FS T2W1 and STIR.

On MR imaging bone bruise is characterized by focal abnormal signal of the bone marrow of femoral condyles or tibial plateau. On T1 weighted images the alterations in signal are characterized by ill-defined low signal intensity. On T2-weighted images these lesions are characterized by areas of high signal intensity. Bone bruise is best differentiated in STIR sequence where the signal of bone marrow fat is significantly suppressed while there is a bright, hyperintense signal of bone bruise.

The meniscal tear is diagnosed as linear or irregular hyperintense signal which can be spread to the margins od hypointense meniscal triangle.

Anterior cruciate ligament injuries are characterized by a low signal intensity on T1-weighted images and hyperintensity of the signal on T2-weigted images. A complete rupture of the ACL is diagnosed when there is a complete lack of the fibers on the ligament spread and the partial rupture when there are some fibers left intact.

For the statistical analysis of the results we used descriptive statistical methods and the Mc Nemar test for the evaluation of statistical significance between the patients with and without bone bruise.

## Results

Bone bruise was seen in 39 (33%) out of 120 patients who had been submitted to MR imaging. In 15 patients bone bruise was located on femoral condyles. Out of these 15 patients, in 13 patients bone bruise was on lateral femoral condyle and in 2 patients on medial femoral condyle (Figure 1a–c). In 11 (28%) patients bone bruise was located on tibial plateau; 7 (18%) patients had both bone bruise on femur and tibia, so-called kissing bone bruises and among them 5 (71%) patients had them in lateral compartment and 2 (29%) patients in medial compartment; 5 (13%) patients had three or more bone bruises and among them 3 patients had them in lateral compartment and 2 in medial (Figure 2).

Overall, bone bruises were more often seen in the lateral than in the medial compartment.

Bone bruise was associated with LCA injury in 27 (69%) patients: more than two thirds of the patients (72%) had lesions of menisci. Out of 28 patients, 4 (14%) patients had lesion of the lateral meniscus, 15 (54%) patients had medial meniscal lesion and 9 (32%) patients had lesions of both menisci; 19 patients or almost half of patients with bone bruise had a combination of bone bruise, ACL and menisci lesions. Only in 2 (5%) patients bone bruise was identified without ACL or menisci pathology (Table 1).

In 3 patients, so-called occult fractures (not seen on plain radiography) were diagnosed.

A total of 78 (65%) patients or of examined patients had no bone bruise while 33 (43%) patients of these 78, had ACL lesion, 49 (63%) patients had menisci lesion, 13 (26%) patients on lateral menisci and 25 (51%) on medial and 10 patients on both menisci.

The differences between the incidence of LCA and lesions of menisci between the patients with and without bone bruise were highly statistically significant ($p < 0.005$) (Table 2).

## Discussion

Bone bruise, as an unique entity on MR, was first identified by Mink et al [12] in 1987. Few years later, bone bruises and occult fractures were divided [13]. Occult fractures usually can not be seen on conventional radiography but have MR characteristics very similar to those of bone bruises with one major difference and that is a disruption of adjacent cortex or osteochondral surface. Conventional radiological techniques are rather limited in showing bone marrow. Because of that, analysis of bone marrow characteristics especially bone bruises, is based on MR imaging. Normal intensity signal of bone marrow is the same as the signal of subcutaneous fat. It is hyperintense on T1-weighted images and medium intense on T2-weighted images. Bone bruise on MR is presented as focal abnormal signal of the bone marrow of the femoral condyles or tibial plateaus. It is seen as a reduction of signal


a)


b)


c)

**a) T1W1 hypointense zone of the medial femoral condyle;**
**b) T2W1 of medium hyperintense zone of medial condyle;**
**c) STIR hyperintense zone of the medial condyle without disruption of the cortex**

**Fig. 1 – Extensive bone bruise of the medial femoral condyle**


**Fig. 2 – Kissing contusion of the medial condyle and medial tibial plateau with smaller subcortical bone bruise on the lateral edge of the lateral tibial plateau on STIR sequence**

**Table 1**

**Distribution of internal knee structure abnormalities in patients with bone bruise**

| Localization | Bone bruise (n = 39) | Localization of the internal knee structure abnormalities (n) | | | | |
|---|---|---|---|---|---|---|
| | | ACL (n = 27) | Men (n = 28) | BMen (n = 9) | MMen (n = 15) | LMen (n = 4) |
| Femur | 15 | 7 | 10 | 2 | 6 | 2 |
| LCon | 13 | 6 | 8 | 2 | 4 | 2 |
| MCon | 2 | 1 | 2 | 0 | 2 | 0 |
| Kissing BB | 7 | 6 | 5 | 1 | 3 | 1 |
| LKiss | 5 | 4 | 3 | 1 | 1 | 1 |
| MKiss | 2 | 2 | 2 | 0 | 2 | 0 |
| Tibia | 11 | 9 | 9 | 4 | 5 | 0 |
| LPla | 7 | 5 | 5 | 2 | 3 | 0 |
| MPla | 4 | 4 | 4 | 2 | 2 | 0 |
| Three and more BB | 5 | 5 | 4 | 2 | 1 | 1 |
| MLat | 3 | 3 | 2 | 1 | 1 | 0 |
| MMed | 2 | 2 | 2 | 1 | 0 | 1 |

**BB – bone bruise; ACL – anterior cruiciate ligamet; Men – meniscus; BMen – Both menisci; MMen – Medial meniscus; LMen – lateral meniscus; LCon – lateral condyle; MCon – medial condyle; LKiss – lateral kissing bone bruise; MKiss – medial kissing bone bruise; LPla – lateral tibial plateau; MPla – medial tibial plateau; MMed – more medial bone bruise; Mlat – more lateral bone bruise**

**Table 2**

**Intraarticular abnormalities in patients with and without bone bruise (BB)**

| Intraarticular abnormalities | Without BB n (%) | With BB n (%) | *p* |
|---|---|---|---|
| Total number of patients | 78 (100) | 39 (100) | $p < 0.005$ |
| Lesion of menisci or ACL | 56 (71.8) | 37 (94.9) | $p < 0.005$ |
| Medial meniscus | 25 (32) | 15 (38.5) | $p < 0.005$ |
| Lateral meniscus | 13 (16.7) | 4 (10) | $p < 0.005$ |
| Both menisci | 10 (12.7) | 9 (23) | $p < 0.005$ |
| ACL | 33 (42.2) | 27 (69.1) | $p < 0.005$ |
| ACL with lesion of menisci | 28 (35.9) | 19 (48.7) | $p < 0.005$ |

**ACL – anterior cruciate ligament**

intensity on T1-weigted images and augmentation of signal intensity on T2-weighted images. The best appearance of bone bruise is described on STIR sequence where the signal of normal bone marrow is suppressed and bone bruise is characterized by the hyperintensity of the signal. This change in signal intensity is caused by posttraumatic edema which is one of the major pathohistological features of bone bruise. The two others are hemorrhage and microtrabecular fracture. Owing to these pathohistological features, it is considered that bone bruise is one of the causes of a painful knee. Owing to the pathohistological analysis of bone bruise, different degrees of subchondral and articular cartilage changes can be observed [13, 14]. Pathogenesis of bone marrow edema which is characteristic for bone bruise is connected with acute or chronic knee injuries, but bone bruises can be seen with no obvious trauma. Bone bruise of the knee usually lasts 12–14 weeks, which is much more than previously thought [15] and sometimes can even be seen up to one year after trauma [16]. Bone bruises associated with posttraumatic lesions of the internal knee structures last more than isolated bone bruises [17]. In the overlying cartilage, degenerative changes including necrosis are described, whereas loss of proteoglycans and different degrees of osteocyte necrosis was seen in the bone matrix. These findings are the basis for further research in the field of late complications of bone bruises such as posttraumatic arthritis [18]. Latest studies show that bone marrow edema seen on MR imaging is a result of different atypical histological changes and that intensity of the signal does not depend only on bone marrow edema [19]. The main finding in bone bruise is posttraumatic edema which is most responsible for signal intensity.

Location and size of bone bruise usually speak for the mechanism of knee injury. Analysis of the force direction can be helpful in analyzing and describing associated knee lesions [9–11]. There are five different mechanisms of knee trauma which give different patterns of bone marrow edema and they are: pivot shift injury, dashboard injury, hyperextension injury, clip injury, and lateral patellar dislocation.

There have not been many studies which analyze the incidence of bone bruises following knee injury [10, 20, 21]. Some of them show the incidence of 20% [22] and some up to 27% [21]. In our study 33% of the patients with knee trauma had bone bruise. Our study was designed so to analyze the presence of bone bruise in acute knee trauma as well as the association with internal knee lesions of LCA and menisci. We analyzed combined posttraumatic lesions of bone marrow, LCA and menisci as very important for acute clinical features and late complications such as osteoarthritis.

In our study the association of bone bruise with injury od LCA was seen in 69% of the patients, similar as in study reported by Davis et al. [15], where they found this association in 67%. This study is very important because MR of the knee was done twice in order to confirm diagnosis. In the study of Lynch et al. [22], bone bruise incidence was 20% and the association with LCA rupture was seen in 77% of the patients. The highest association of bone bruise with LCA rupture was seen in study of Atkinson et al. [17] and it was 78%. The term LCA injury is used because in our study we had no arthroscopy done in our patients in order to distinguish partial from a complete rupture of the anterior cruciate ligament. Under the term “menisci injury” or “menisci lesion” we consider all pathological posttraumatic MR findings such as traumatic tears as well as degenerative posttraumatic changes without grading menisci degeneration in three degrees (degree 1, 2, 3). In our study the association of bone bruise with menisci lesions was observed in 72% of the patients. It is very important to emphasize that in acute knee injury it is very hard to distinguish traumatic menisci tears from the degenerative ones which was not the aim of our study.

Cothran et al. [23] were the first to introduce the MR characteristics of posttraumatic contusion menisci lesions. It is therefore essential to consider menisci lesions not only as a cause of a painful knee and a diminished knee function but also as a predictor of further osteoarthritis [24]. There have been many studies with the aim to confirm the associations of bone bruise and LCA lesions. Almost all analyzed this association but placing LCA as primary outcome for the study. There have been fewer studies which analyze the association of bone bruises and menisci lesions [17, 25]. Our study analyzed both the association of bone bruise and the internal knee structures lesions but placing bone bruise finding as primary.

## Conclusion

Bone bruise is a very common finding in acute knee injury. It is more often on the lateral knee compartment. In acutely injured knee, bone bruise can indicate the injury pattern and it can be very helpful in detecting associated posttraumatic internal knee lesions. By the precise analysis of bone bruise and the pattern of bone injury we can focus on analysis of internal knee structures lesions. The golden stan-

dard for visualizing posttraumatic contusion knee lesion on MR is the STIR sequence. In this way finding of bone bruise on MR leads to finding the expected but less well seen lesions of internal structures of the knee. Patients with bone bruise have significantly more lesions of LCA and menisci than patients without bone bruise.

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Received on February 1, 2010.
Revised on November 15, 2010.
Accepted on November 16, 2010.

ORIGINAL ARTICLE

UDC: 616.441-08
DOI:10.2298/VSP1109767A

# Possibilities of nontoxic autonomous thyroid nodules treatment by percutaneous ethanol injection

## Mogućnosti lečenja netoksičnih autonomnih čvorića tiroideje perkutanim ubrizgavanjem etanola

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**Abstract**

**Background/Aim.** According to the current principles, autonomous functional thyroid nodules are treated by surgery or by radioiodin therapy. Ultrasound guided percutaneous ethanol injection into solid tumors of the soft tissues was a starting point in attempts to treat the thyroid nodules by the same method. The aim of the study was to assess the efficiency of percutaneous injection in treating solitary, nontoxic, autonomous thyroid nodules of up to 15 mL volume. **Methods.** In 25 patients with solitary nontoxic autonomous thyroid nodules diagnosed by tehnetium-99m scanning as an intensive area having a complete supremacy in the paranodal tissue, an ultrasound guided percutaneous ethanol injection was applied. The procedure was carried out repeatedly once a week until the reduction in nodule size to 50% of the initial size was achieved. **Results.** An average size of the nodule before curing was 9.68 ± 5.01 mL. An average quantity of the injected ethanol was 9.52 ± 5.08 mL, *ie* 1.06 ± 0.48 mL/mg of the tissue. The regression of the nodule size in the successfully (Δvol% u = -57.09 ± 13.75%, $p < 0.001$) and partly successfully cured (Δvol du = -48.45 ± 14.35%, $p < 0.05$) was statistically significant compared to the size before the treatment. After ceasing ethanol injection, 18 months later, a further size regression (Δvol% = -79.20 ± 9.89%) compared to the initial one ($p < 0.001$) was noticed. Soon, after the procedure was finished, a statistically significant concentration increase of Thyroid Stimulating Hormone (TSH) was noticed compared to the initial values (0.18 ± 0.16 *vs* 0.34 ± 0.31 mU/L, $p < 0.01$). According to the given criteria, in two female patients satisfactory results were not achieved, but, a year later, in one of them the nodule was not seen by repeated scintigram. The number and frequency of side effects were insignificant. **Conclusion.** Repeated percutaneous ethanol injections into nontoxic solitary autonomous thyroid nodules result in disappearing of authonomy. The regression of the nodule size of more than 50% compared to its initial volume, as well as the increase in concentration of TSH for more than 50% are the signs of a successful treatment.

**Key words:**
**thyroid diseases; thyroid hormones; goiter, nodular; ethanol; ultrasonics.**

**Apstrakt**

**Uvod/Cilj.** Prema sadašnjim principima, autonomni funkcionalni tiroidni nodusi leče se operativno ili terapijskom primenom radioaktivnog joda. Perkutana, ultrazvučno vođena aplikacija etanola u solidne tumore mekih tkiva bila je polazna osnova za pokušaje lečenja tiroidnih nodusa istom metodom. Cilj ovog rada bio je da se ocene terapijski efekti perkutane aplikacije etanola kod solitarnih, netoksičnih autonomnih tiroidnih nodusa zapremine do 15 mL. **Metode.** Kod 25 bolesnika sa solitarnim netoksičnim nodusima koji se scintigrafski (tehnecijum 99m) intenzivnije prikazuju i potpuno suprimiraju paranodalno tkivo, uz pomoć ultrazvuka perkutano je aplikovan etanol. Procedura je ponavljana u sedmičnim intervalima dok nije ostvarena redukcija veličine nodusa od 50% u odnosu na početnu vrednost. **Rezultati.** Prosečna veličina nodusa pre lečenja iznosila je 9,68 ± 5,01 mL. Prosečna količina aplikovanog etanola iznosila je 9,52 ± 5,08 mL, odnosno 1,06 ± 0,48 mL/mg tkiva. Regresija veličine nodusa kod uspešno (Δvol% u = -57,09 ± 13,75%, $p < 0,001$) i delimično uspešno lečenih (Δvol du = -48,45 ± 14,35%, $p < 0,05$) bila je statistički značajna u odnosu na veličinu pre lečenja. Po prestanku aplikacija etanola, nakon 18 meseci uočena je dalja regresija veličine nodusa (Δvol% = -79,20 ± 9,89%) u odnosu na početnu ($p < 0,001$). Neposredno nakon završene procedure registrovan je statistički značajan porast koncentracije tireostimulirajućeg hormo-

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na (TSH) u odnosu na početne vrednosti (0,18 ± 0,16 *vs* 0,34 ± 0,31 mU/L, $p < 0,01$). Prema zadatim kriterijumima kod dve bolesnice nisu ostvareni zadovoljavajući efekti lečenja, s tim što se kod jedne, nakon godinu dana, na ponovljenom scintigramu nodus više nije prikazivao. Broj i učestalost neželjenih efekata bio je zanemarljivo mali. **Zaključak.** Ponavljane perkutane aplikacije etanola u netoksične solitarne autonomne noduse štitaste žlezde dovode do isčezavanja autonomije. Regresija veličine nodusa za više od 50% u odnosu na početni volumen, kao i porast koncentracije TSH za više od 50%, pokazatelji su uspešnog ishoda lečenja.

**Ključne reči:**
**tireoidna žlezda, bolesti; tireoidna žlezda, hormoni; gušavost; etanol; ultrazvuk.**

## Introduction

Solitary autonomous functional thyroid nodules (AFTN) are parts of thyroid parenchymas which in functional and in the sense of controlling growth act separately from the regulatory action of hypophysis, *ie* thyroid stimulating hormone (TSH). Laboratory criterion for diagnosing is an inability to suppress the function of nodules by suppressive doses of thyroid hormones. At the same time, the suppressed paranodal tissue has retained the ability to answer the stimulation by exogenous giving TSH. Unlike toxic ones, nontoxic nodules have normal serum levels of thyroid hormones.

According to the current principles, toxic nodules are treated surgically or with therapeutic application of radioactive (RA) iodine. The need for curing the nontoxic AFTNs is based on the observation that most of the ill have subnormal TSH levels and, hence, subclinical hyperthyreosis. On the other hand, taking larger quantities of iodine, which occurs when giving iodine contrast media, the drugs containing iodine, or when eating food rich in iodine, multiplies the possibility of evolution of nontoxic nodules into the toxic ones.

The results achieved by the use of ethanol in treatement of hepatocellular carcinomas [2] and benign cysts in the thyroid gland [3] were a starting point for the attempts to cure the autonomous nodules by the same method. The procedure of percutaneous ethanol injection (PAE) into the nodules of thyroid gland was promoted at the beginning of the 1990s. Then, there were the first results published of treating eight patients in this way in whom the regression in nodules size and the disappearance of autonomy [4] were achieved, regardless a small number of ethanol injections. Later observations of a few tenths to over a hundred patients who were followed during long intervals (4–8.5 years) proved good effects of curing. In the largest number of the cured, PAE led to a complete or a partial curing, with a very small number of recidives. In a certain number of patients (about 12%), mainly with toxic nodules, there were no results of curing [5–7].

In an attempt to contribute to the achievements which would make this method generally accepted we started with the fact that there was not a single study with a selection of patients regarding the autonomy level, as well as that most studies included heterogeneous groups of patients with nodal, polynodal, most often toxic nodules of various sizes.

The aim of this study was to estimate therapeutical effects of 15 mL percutaneous ethanol injection in patients with nontoxic, solitary AFTNs, which most often occur in clinical practice.

## Methods

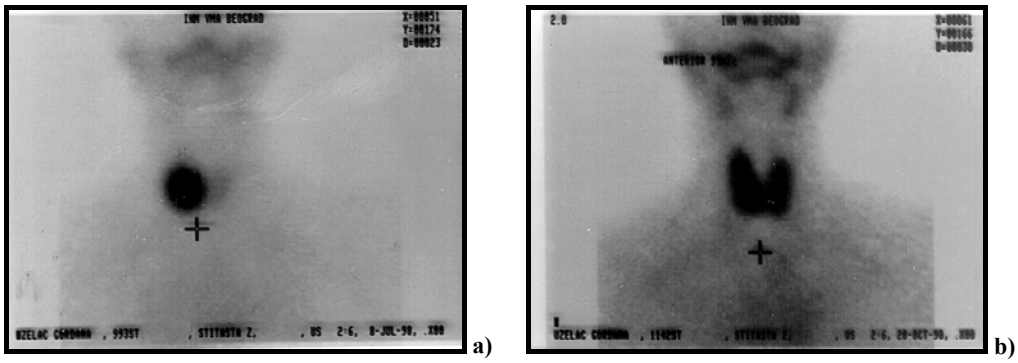
The study included 25 patients with solitary nodules which appeared more intense on scintigraphy (Te-99m) and had a complete supremacy in paranodal tissue. According to serum concentration of thyroid hormones and TSH, the patients with toxic nodules were excluded. By cytological analysis of aspirates from nodules any doubts of malignancy were eliminated.

A Hewlett Pacard apparatus with a linear probe of 7.5 MHz was used for echotomographic estimation and controlling the injection. The volume of nodules was calculated according to the formula for ovoid: $V = \pi/6 \times A \times B \times C$ (A – craniocaudal, B – anteroposterior, C – mediolateral nodule diameter) and it was expressed in millilitres, *ie* milligrams of tissue. The amount of the injected ethanol per seance was not determined in advance, but ethanol was injected up to the point of perfusion and not more than 2/3 of the visible surface of the nodule. Color Doppler was used to direct the injection into the areas with the largest number of exposed capillaries. The quantity of ethanol determined in this way was expressed in mL of ethanol/mL (mg) of the nodule tissue. The injections were done in the outpatient department, repeatedly, at intervals of once a week.

With the aim to estimate the effects, control scintigraphy was carried out on condition that the following three criteria were fulfilled: regression of nodule volume to at least 50% compared to the initial one; significantly changed echotomographic structure of the nodule with the earlier hypoechographic fields disappearing; when not a single exposed capillary within the nodule could be seen on colour Doppler.

The effects of treatment were defined as: successful (s), partly successful (ps), and unsuccessful (u), the scintigraphic finding being a determiner. Criteria for estimating success of treatment were: disappearance of all clinical manifestations of the illness; increase in concentration of TSH for at least 50% compared to its level before treatment; decrease in nodule volume for 50% compared to the initial one; scintigraphic finding on which the earlier suppressed paranodal tissue is completely shown (Figure 1 a, b). Partly successful: the patients with three of the four formerly mentioned criteria fulfilled. Unsuccessful: only two of the four mentioned criteria fulfilled.

All immediate side effects were noticed, as well as their persistence. The examination was carried out according to the principle of prospective clinical study. All the patients were introduced to the procedure and the aim of treatment, and only those who agreed to be treated on this way were in-



**a) b)**

**Fig. 1 – Scintigraphic findings: a) appearance before and b) afther the successful treatment with percutaneous ethanol injection**

cluded in the study. The criterion for excluding the patients was their own decision.

All the results in tables were shown as an average value ± standard deviation ($\bar{x} \pm SD$). Depending on the distribution of features, statistical importance among the groups was estimated by the Student's *t*-test or by the Mann-Whitney *U*-test. Comparison of the frequencies, depending on their location, was made by using $\chi^2$-test or by Kolmorogov-Smirnov test. Connection with various features was tested by using the Pearson's correlation quotient. A statistically singificant difference in the groups was defined on the three levels of possibilities: $p < 0.05$; $p < 0.01$ and $p < 0.001$.

## Results

The procedure was applied on 25 patients (23 women and 2 men), 19–76 (47.18 ± 16.3) years of age. An average nodule volume before treatment was 9.68 ± 5.01 mL. As for echo structure, 64% (16/25) of those being cured had a clearly parenchymatous structure, while 36% (9/25) had nodules with the signs of cystic degeneration. Regardless echo structure, all the nodules showed diffusionally accentuated vascularisation.

An average quantity of the injected ethanol was 9.52 ± 5.08 mL *ie* 1.06 ± 0.48 mL/mg of tissue. Injection rate was 4 to 12 applications.

The regression of nodules was expressed in percents of nodules diminishing at the end of treatment compared to their initial volume (Δvol %). In all the patients, a statistically significant diminishing of nodules volume was achieved, being slightly larger nodules with the signs of cystic degeneration (Table 1).

As for the results, the successfully (Δvol% s = -57.09 ± 13.75%, $p < 0.001$) and partly successfully cured (Δvol ps = 48.45 ± 14.35%. $p < 0.05$) showed a statistically singificant difference in diminishing as compared to nodules volume before the treatment. Although the successfully cured, compared to the partly successfully cured ones, showed a higher level of volume diminishing, this difference was not statistically singificant. However, if nodules volumes were expressed in milliliters, we would find a higher level of nodule size regression in the successfully cured than in the partly successfully cured ones. This difference is statistically singificant (s = 3.17 ± 1.24 *vs* ps = 3.17 ± 1.24 mL $p < 0.01$) (Table 2; Figures 2a, b and 3 a, b and c).

After stopping ethanol injection, all the patients were followed during the next 18 months. Control examinations were done every 6 months. Nodules volume reduction after 18 months was Δvol% = -79.20 ± 9.89% as compared to the initial one ($p < 0.001$) (Table 3).

The function of the thyroid gland was estimated by measuring the levels of thyroid hormones: triodothyronine (T3), tyroxine (T4), TSH and tyreoglobulin (Tg). The values were controlled before, immediately after finishing the procedure and after 6, 12, and 18 months following finishing the injection (Table 4, Figure 4).

**Table 1**

**Nodules volume before and after percutaneous ethanol injection in realtion to echo structure**

| ECHO structure | Nodules volume, $\bar{x} \pm SD$ (mL) | | | Δvol (%), before/after |
|---|---|---|---|---|
| | Before | ← *p* → | After | |
| Parenchymatous | 7.90 ± 3.31 | 0.001 | 3.78 ± 1.99 | -52.08 ± 13.69 |
| Cyst.degener. | 12.84 ± 6.11 | 0.01 | 5.57 ± 3.47 | -55.26 ± 16.36 |
| *p* | < 0.05 | | *ns* | *ns* |

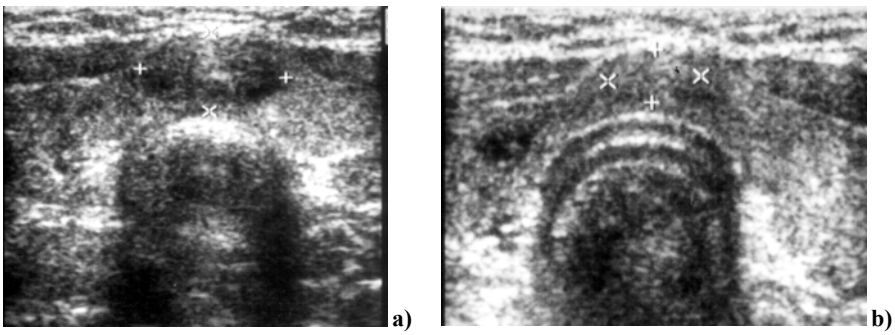
***ns* – non significant**

**Table 2**

**Nodules volume before and after percutaneous ethanol injection in relation to outcomes of the treatment**

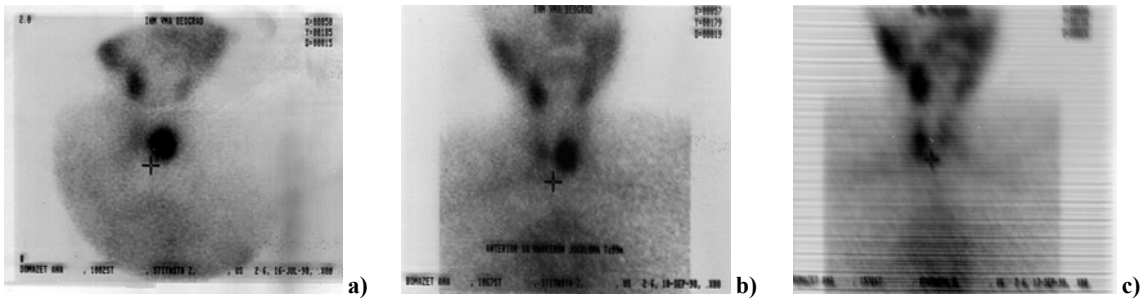
| Treatment outcome | Nodules volume, $\bar{x} \pm SD$ (mL) | | | Δvol (%), before/after |
|---|---|---|---|---|
| | Before | ← *p* → | After | |
| Successfull | 7.91 ± 3.68 | 0.001 | 3.17 ± 1.24 | -57.09 ± 13.75 |
| Partly successfull | 12.70 ± 6.39 | 0.05 | 6.20 ± 3.11 | -48.45 ± 14.35 |
| *p* | *ns* | | < 0.01 | *ns* |

***ns* – non significant**



**a) b)**

**Fig. 2 – Echotomographic appearance of AFTN: a) before and b) after successful treatment with percutaneous ethanol injection**



**a) b) c)**

**Fig. 3 – Scintigraphic appearance of a nodule in the left lobe of the thyroid before, immediatly after percutaneous ethanol injection (a and b) and one year later (c)**

**Table 3**

**Nodules volume (%) at the begining and Δvol(%) during 18 month period**

| Time period (month) | Nodules volume (mL) | Δvol (%) |
|---|---|---|
| 0 | 9.68 ± 5.01 | – |
| 6 | 3.55 ± 2.44‡ | 63.00 ± 13.36 |
| 12 | 3.19 ± 2.21† | 70.70 ± 12.08 |
| 18 | 2.51 ± 2.51* | 79.20 ± 9.89 |

***p* < 0.05; †*p* < 0.01; ‡*p* < 0.001 in relation to the value at the begining (0)**

**Table 4**

**Function of the thyroid gland during 18 month period**

| Time period | Thyroid hormones levels | | | |
|---|---|---|---|---|
| | T3 (nmoL/L) | T4 (nmoL/L) | TSH (IJ/L) | Tg (μg/L) |
| Before | 2.84 ± 0.97 | 156.32 ± 54.68 | 0.18 ± 0.16 | 62.84 ± 39.13 |
| After | 2.33 ± 0.49* | 140.92 ± 31.52 | 0.34 ± 0.31† | 108.32 ± 44.70‡ |
| 6 months | 1.87 ± 0.40‡ | 124.21 ± 14.96† | 0.69 ± 0.40‡ | 38.49 ± 26.70† |
| 12 months | 1.97 ± 0.28† | 128.17 ± 12.97 | 0.77 ± 0.44† | 33.50 ± 16.18† |
| 18 months | 1.90 ± 0.38* | 126.62 ± 15.26 | 1.12 ± 0.39* | 25.95 ± 23.53* |

***p* < 0.05; †*p* < 0.01; ‡*p* < 0.001 in relation to levels at the begining**
**Normal levels: T3 = 1.2 - 2.8; T4 = 60 – 160; TSH = 0 – 4; Tg = up to 50**

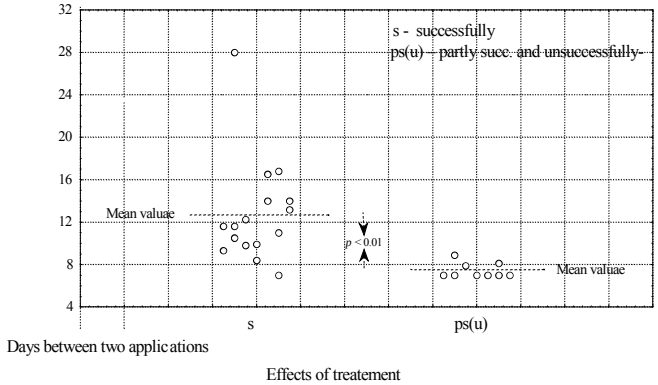



**Fig. 4 – Treatment success in relation to the number of days between the two aplications of etanol**

**Discussion**

Autonomous thyroid nodules represent 5%–10% of all palpable or in other ways recognisible thyroid nodules. There are a few phases in the development of AFTN. First, there appears a functional nodule without an autonomy. In its further evolution it can grow into an autonomus hyperfunctional or toxic tyroid nodule. In the controlled, prospective clinical studies it is shown that after a 5-year follow up, 15%–20% of the autonomous nodules larger than 3 cm become toxic [8, 9], and that they are treated with either surgery or therapeutical application of RA iodine. In treatment nontoxic AFTN is still a subject of discussion, with a number of objections. The opposite attitudes are problematic promoting either clinical following or surgical treatment. Those who are for clinical following base their attitude on the fact that only a small number of AFTNs evoluate into the toxic ones, as well as that the possibility of malignancy is slight [10, 11].

During the last 20 years or so, ultrasound guided percutaneous ethanol injection has become a successful way of curing both malignat and benign soft tissue tumors. The principle of treatment is based on the knowledge that after injecting ethanol regularly spreads within the tumor lesion by diffusion and, then, it causes an inactivity of the oxidative enzymes, dehydration of the cells, denaturation of proteins, venous microthrombosis and coagulation necrosis followed by fibrosis [12]. The surrounding tissue is saved since it appears that ethanol stays within the tumor lesion. The first reports of positive effects refer to local ethanol injection into hepatocellular carcinomas derived from cirrhosis of the liver [2]. Inactivation of parathyroid adenomas by ethanol appeared to be successful in an important number of those having primary hyperparathyroism and, in some cases, after an unsuccessful surgical exploration, it can be the only possible choice of treatment [13, 14]. Sclerosing of benign cystic nodules in the thyroid gland has been used for a long time, and there are more and more proofs of reduction in its size and therapeutical efficiency of PAE in the treatement of benign solid nodules [15].

Percutaneous ethanol injection was introduced into clinical practice by Livraghi et al. [16] in 1990. It was shown then that regression in nodule size, followed by disappearance of autonomy, was achieved, despite a small number of ethanol injections. Later examinations of a larger number of patients who were followed over longer time intervals proved positive effects of this way of curing with only a slight number of complications [5–7]. It was also shown that subclinical hyperthyreosis was corrected in all, while the manifested one was cured in 52%–80% of patients, with only a slight number of recidives. The achieved nodule size regression was from 21% to 88% compared to the initial size.

In our group of patients there were 16 (64%) successfully treated, 7 (28%) partly successfully treated, while in 2 (8%) patients the treatment had no effect. Despite the fact that the criteria for estimation success in the results were very strict, looking for the reasons for such results we started with the question whether nodule volume had an effect on the results of treatment. The attitudes concerning the connection between nodule size and the results of treatment, according to the current knowledge, are not completely unique. There prevails an attitude that nodule size only partly affects the results of treatment. Best results were achieved in nontoxic AFTN the volume of which was not bigger than 10–13 mL [16–18]. Average nodule volume in our patients was $9.68 \pm 5.01$ mL where the cystic degenerated nodules had quite a bigger volume compared to the parenchymatous ones. Regarding the results, the nodules which were partly cured and unsuccessfully cured were bigger in comparison with the successfully cured ones. This difference, however, was not statistically singificant (Vol ps + u > Vol s; *ns*). The cited results led to a conclusion that the nodules of smaller volumes could be cured more easily. However, by linear regressive analysis the correlation between the nodule volume and the results of treated was not proved. It was shown that the degree of nodule vascularisation had far greater importance for a successful curing. It was noticed that during the treatment, at the time of the planned ultrasound controls, the shape of vascularisation changed in that way that the blood flow gradually weakened, first within parenchyma, and later around the edge of the nodule. At the end of the procedure, in the successfully cured, both types of vascularisation completely disappeared. Together with the lower blood flow we noticed a regression in nodule size and appearance of fibrosis in parenchyma. The explanation for this could lie in the noticed occurence that the well vascularised nodules made possible a quicker and a more regular distribution of the injected ethanol, so that even the small amounts of the injected ethanol reached evenly all the parts of nodules and caused the tissue degradation.

Reduction in nodules size was expressed in percents at the end of treatment compared to their initial volume (Δvol%). We first noticed the good effects of ethanol injecting by the signs of reducting in nodules volume, and we also took into consideration the personal sensation of the patients at control examinations. Size regression represents the occurence about which there is the smallest number of disagreements in the literature. There is a generally accepted attitude that the direct effect of ethanol is first to be recognised according to the nodules size reduction which, depending on the duration of the follow-up, was from 20% [19] even up to 81%–93% [20, 21] compared to their initial size. Does Δvol% have an effect on the results of treatment? Similar to some other authors [20], by following our patients we noticed that nodules with the positive results of curing had a bigger Δvol% in comparison with the nodules with the partly successful and unsuccessful results of treatment. We started with the supposition that if a greater size reduction was achieved during therapy there was a greater possibility of getting positive results of curing. We checked our supposition by linear regressive analysis and proved a linear correlation between the degree of regression and the nodule size and, hence, the success of curing ($r = -0.2594$, $p < 0.05$). Despite the proved linear correlation between the degree of regression and nodule size and the success of curing, comparisons within the group offered us some interesting ideas and conclusions. Out of 25 patients, 16 (64%) were successfully cured, 7 (28%) were partly successfully cured and 2 (8%)

were unsuccessfully cured. After comparing Δvol% of the successfully cured with the partly successfully and unsuccessfully cured there was found no statistically singificant difference. Looking for the reasons of curing to be successful in some patients, but partly successful or unsuccessful in other we analysed some characteristics of nodules and the curing procedures. Nodules in the subgroup of the successfully treated were of smaller dimensions compared to the unsuccessfully treated but this difference was not statistically singificant. So, we could not accept nodules size as a reason for the unsuccessful results of curing. Both subgroups did not differ in ultrasound structure of the nodules, the ways of vascularisation, the quantity of the injected ethanol and the number of injections. A statistically singificant difference was noticed in only the time intervals between the two injections. In the successfully cured, a period between the two injections was 12.7 days on average, and in the partly successfully treated and unsuccessfully treated 7.43 days ($p < 0.01$). The difference in a period between the two ethanol injections was made on purpose as the result of the first experiences during the introduction of the procedure into practical work. Namely, very early it was noticed that the nodule size regression continued even after ceasing ethanol injection. It appeared that a year following ceasing ethanol injection nodules regressed another 16% in comparison with their volume at the end of curing. We supposed that for the occurence of a number of involutive changes, from cytochemical to fibrosal ones, a certain period of time was necessary. Having that in mind, there is a small possibility that a larger quantity of the injected ethanol would fasten, or that a smaller quantity would slow down this process which has its logical sequence, from functional to definite morphological changes. We supposed that the newly injected quantity of ethanol only perpetuated the process of degradation and continued progression towards final necrosis and replacement by a fibrotic tissue. Considering the first noticing in mind and thinking in this way, we controlled all the patients weekly, but we adjusted ethanol injection individually to a period from 2 to 3 weeks, giving chance to the previously injected ethanol to do its function of destruction. We followed our patients 18 months after finishing the treatment. Despite stopping ethanol injections, further regression in size was noticed, which proved the cited suppositions and conclusions.

In the patient with the results of curing initially defined as unsuccessful, with already described clinical findings, after a year, during repeated scintigraphy, the nodule was not visible any more. We suppose that quite probably, after a period of time, in all the patients who were partially treated (as they were classified at the end of ethanol injection), the results of scintigraphy approved the disappearance of the autonomy.

By observing the thyroid gland function, an increase in TSH was noticed as a sign of autonomy disappearance, and as the proof of a successful treatment. The values of Tg immediately after the end of curing showed an increase in value which we considered was due to degeneration in nodule tissue. In the later course, with the development of fibrosis and regression of the size, Tg values lowered, too.

Carrying out PAE is primarily based on the skill and experience of the doctor who applies the procedure which, to some extent, causes the appearance and content of side effects. Some of them, such as pain, overflowing of the thyroid hormones into circulation, and the development of thyroid antigen are justifiably present and are the consequence of a direct contact of ethanol with the nodule tissue. In our series of patients, the side effects of the procedure were milder and did not disturb further carrying out or possible ceasing of therapy. The degree of discomforts that appeared and the definition of the efficiency of treatment were estimated on the basis of the questionnaire which was filled in by the patients at the end of therapy, and their intensity was ranged by the index from 1 to 5. In 91.3% of the treated patients there was pain and burning at the site of injection of an average intensity of 2.7 index points. In nearly one half of the treated (43.47% to 52.17%) pain spreaded to the jaw, shoulder, chest and ear, and it was marked with the index from 1.08 to 1.26. The appearance of local and/or projected pain, as it can be seen, represents an inevitable manifestation of the procedure. Luckily, these manifestations which can, to some extent, complicate the procedure, had a very weak intensity. Nearly 10% of the treated did not feel pain, or, what was more likely, they did not consider it an important side effect. It seems that the intensity of pain and its eventual further spreading mostly depend on the location of the nodule, its ultrasound structure and its vicinity to the thyroid capsule. Pain was less severe in cystically degenerated nodules compared to the ones with parenchymal structure, but it became more intense as the number of injections grew and with the appearance of sclerosis within the nodule. Then, it was practically impossible to prevent overflowing of even small quantities of ethanol extranodally. Thyroid capsule seems to be the best innerved part of the thyroid since curing nodules in its vicinity was most painful, and pain always spreaded away, most often as far as the temporomandibular joint and ear. In nodules localized quite near the lower pole of the thyroid lobe propagation of pain went along the middle chest or into shoulder. The mentioned discomforts were temporary and mainly lasted short. Thus, in 86.9% of the treated the discomforts were present for only a few hours after injection while in 13.1% of patients they prolonged until the next day. A slight number of patients reported having difficulty with moving their neck, an occiput headache and a temporary sense of slackening of vigour, as described by other authors.

## Conclusion

It can be concluded that repeated percutaneous ethanol injections into nontoxic solitary autonomous thyroid nodules lead to autonomy disappearance. Regression in nodule size for more than 50% as compared to the initial one, as well as the growth of concentration of TSH for more than 50% are the signs of success in therapy. Nodule size does not affect either the result of curing or the quantity of the injected ethanol. Side effects of the procedure are rare and directly depend on the experience of the doctor carrying out the procedure.

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Received on February 23, 2010.
Accepted on March 1, 2010.

ORIGINAL ARTICLE

UDC: 617.3:[616-0721::617.583
DOI:10.2298/VSP1109774D

# Arthroscopic partial medial meniscectomy

## Artroskopska parcijalna medijalna meniscektomija

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**Abstract**

**Background/Aim.** Meniscal injuries are common in professional or recreational sports as well as in daily activities. If meniscal lesions lead to physical impairment they usually require surgical treatment. Arthroscopic treatment of meniscal injuries is one of the most often performed orthopedic operative procedures. **Methods.** The study analyzed the results of arthroscopic partial medial meniscectomy in 213 patients in a 24-month period, from 2006, to 2008. **Results.** In our series of arthroscopically treated medial meniscus tears we noted 78 (36.62%) vertical complete bucket handle lesions, 19 (8.92%) vertical incomplete lesions, 18 (8.45%) longitudinal tears, 35 (16.43%) oblique tears, 18 (8.45%) complex degenerative lesions, 17 (7.98%) radial lesions and 28 (13.14%) horisontal lesions. Mean preoperative International Knee Documentation Committee (IKDC) score was 49.81%, 1 month after the arthroscopic partial medial meniscectomy the mean IKDC score was 84.08%, and 6 months after mean IKDC score was 90.36%. Six months after the procedure 197 (92.49%) of patients had good or excellent subjective postoperative clinical outcomes, while 14 (6.57%) patients subjectively did not notice a significant improvement after the intervention, and 2 (0.93%) patients had no subjective improvement after the partial medial meniscectomy at all. **Conclusion.** Arthroscopic partial medial meniscetomy is minimally invasive diagnostic and therapeutic procedure and in well selected cases is a method of choice for treatment of medial meniscus injuries when repair techniques are not a viable option. It has small rate of complications, low morbidity and fast rehabilitation.

**Key words:**
**menisci, tibial; wounds and injuries; arthroscopy; postoperative complications; treatment outcome.**

**Apstrakt**

**Uvod/Cilj.** Povrede meniskusa su česte u profesionalnom i rekreativnom sportu, kao i tokom svakodnevnih aktivnosti. Lezije meniskusa obično zahtevaju hirurško lečenje ukoliko dovedu do smanjenja fizičke sposobnosti. Artroskopsko lečenje povreda meniskusa jedna je od najčešće izvođenih ortopedskih operativnih procedura. **Metode.** U radu su prikazani rezultati artroskopske parcijalne medijalne meniscektomije izvedene kod 213 bolesnika u periodu od 24 meseca, od 2006. do 2008. godine. **Rezultati.** U našoj seriji artroskopski tretiranih lezija medijalnog meniskusa bilo je 78 (36,62%) vertikalnih kompletnih *bucket handle* lezija, 19 (8,92%) vertikalnih nekompletnih lezija, 18 (8,45%) longitudinalnih raskida, 35 (16,43%) kosih raskida, 18 (8,45%) kompleksnih degenerativnih, 17 (7,98%) radijalnih raskida i 28 (13,14%) horizontalnih lezija. Srednji preoperativni *International Knee Documentation Committee* (IKDC) skor bio je 49,81%, mesec dana nakon parcijalne artroskopske medijalne meniscektomije srednji IKDC skor bio je 84,08%, a 6 meseci nakon operacije srednji IKDC skor bio je 90,36%. Šest meseci nakon procedure 197 (92,49%) bolesnika imalo je dobar ili odličan postoperativni ishod, 14 bolesnika (6,57%) subjektivno nije imalo značajno poboljšanje nakon intevencije, a dva bolesnika (0,93%), nisu imala nikakva subjektivna poboljšanja nakon parcijalne artroskopske meniscektomije. **Zaključak.** Artroskopska parcijalna medijalna meniscektomija je minimalno invazivna dijagnostičko-terapijska procedura. Kod dobro odabranih bolesnika, i kada tehnike reparacije nisu primenjive, predstavlja metod izbora za lečenje povreda medijalnog meniskusa. Prati je niska učestalost komplikacija, nizak morbiditet i brza rehabilitacija.

**Ključne reči:**
**meniskus tibije; povrede; artroskopija; postoperativne komplikacije; lečenje, ishod.**

### Introduction

The mean annual incidence of meniscal tears is 60 to 70 per 100 000 [1]. Meniscal tears are more common in males. The male : female ratio ranges from 2.5 : 1 to 4 : 1. Meniscal injuries are a common problem in sports and they are the most frequent injury to the knee joint. Such injuries are especially prevalent among competitive athletes, particularly

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those who play football, basketball, volleyball and sometimes tennis. In the past 25 years, with increasing popularity of professional and recreational sports the number of people participating in sports has greatly increased, resulting in a higher number of knee injuries [2]. If meniscal lesions lead to physical impairment they usually require surgical treatment. Arthroscopic treatment of meniscal injuries has become one of the most often performed orthopedic operative procedure. In order to properly diagnose and treat meniscal injuries, understanding of meniscal anatomy and function is necessary.

Medial meniscus is C-shaped, with the posterior horn larger than the anterior horn in the anteroposterior dimension. Johnson et al. [3] mapped the bony insertion sites of the meniscus. They noted that the anterior horn of the medial meniscus has the largest insertion site surface area (61.4 $mm^2$) and the posterior horn of the lateral meniscus, the smallest (28.5 $mm^2$). The capsular attachment of the medial meniscus on the tibial side is referred to as the coronary ligament. A thickening of the capsular attachment in the midportion spans from the tibia to the femur and is referred to as the deep medial collateral ligament.

The meniscus has a fibrocartilaginous structure. The orientation of collagen fibers is mainly circumferential, with some radial fibers at the surface and within the midsubstance. This orientation allows compressive loads to be dispersed by the circumferential fibers, while the radial fibers act as tie fibers to resist longitudinal tearing. Collagen is 60% to 70% of the dry weight of the meniscus. The majority of collagen (90%) is type I, with types II, III, V, and VI present in much smaller amounts. Elastin accounts for approximately 0.6% and noncollagenous proteins, for 8% to 13% [4]. The cells of the meniscus are fibrochondrocytes because of their appearance and the fact that they synthesize a fibrocartilaginous matrix.

The menisci are important in many aspects of knee function, including load sharing, shock absorption, reduction in joint contact stresses, passive stabilization, increasing congruity and contact area, limitation of extremes of flexion and extension and proprioception [5]. Many of these functions are achieved through the ability of the menisci to transmit and distribute load over the tibial plateau. The medial and lateral menisci transmit at least 50% to 70% or at times more of the load when the knee is in extension; this increases to 85% with 90° of knee flexion [6]. Removal of the medial meniscus results in a 50% to 70% reduction in femoral condyle contact area and in a 100% increase in contact stress [7].

The onset of symptoms and mechanism of injury were often of utmost importance for the diagnosis. Meniscal lesions often occured during a rotational injury or hyperflexion event, and they in most cases presented with acute pain and swelling. Complaints of locking or catching were also present, and loss of motion with a mechanical block to extension [8]. Degenerative tears of the medial meniscus were mostly noted in older patients (> 40 years). These tears were often associated with some degree of osteoarthritis.

Though not always absolutely exact clinical evaluation is a very useful tool in the diagnosis of meniscal pathology. Weinstabl et al. [9] found that joint line tenderness was the best clinical sign of a meniscal tear, with a 74% sensitivity and 50% positive predictive value.

Plain radiographs should be obtained before any further diagnostic studies are undertaken, although these radiographic views cannot confirm the diagnosis of meniscal lesion, they are important in defining bony pathology and in evaluating the knee for joint space narrowing.

Magnetic resonance imaging is the imaging method of choice for diagnosing meniscal tears [10]. Accuracy for detecting meniscal tears was commonly reported at 80% to 90% [11]. With improved technology and increased experience in reading these scans, the accuracy of detection is now considered to be approximately 95% or better [12].

Classification of meniscal lesions-commonly described patterns of meniscal lesions include vertical (complete vertical – bucket handle tears) or incomplete – longitudinal, oblique, often called flap or parrot beak tears, complex – including degenerative, transverse (radial) and horizontal. With increasing age, degenerative complex tears are more frequently seen.

Surgical indications for arthroscopic treatment of meniscal pathology include: symptoms of meniscal injury that affect activities of daily living, work and/or sports, positive physical findings of joint line tenderness, joint effusion, limitation of motion and provocative signs, such as pain with squatting or a positive flexion McMurray or Apley grind test, failure to respond to nonsurgical treatment, including activity modification, medication, and a rehabilitation program, and the absence of other causes of knee pain identified on plain radiographs or other imaging studies.

Osteoarthritic changes after meniscectomy have been reported in up to 89% of patients [8]. Numerous studies have shown that knee osteoarthritis is more common after total meniscectomy, and that partial meniscectomy is assotiated with less radiographic and clinical signs of osteoarthritis over time compared with total meniscectomy [9–13]. Crawford et al. [14] showed that the International Knee Documentation Committee (IKDC) score has an overall acceptable psychometric performance for outcome measures of meniscus injuries of the knee. The aim of the study was to demonstrate that arthroscopic partial medial meniscetomy in well selected cases is a method of choice for treatment of medial meniscus injuries that are not amenable to repair, because it has small rate of complications, low morbidity and fast rehabilitation.

## Methods

This study analyzed the results of arthroscopic partial medial meniscectomy in 213 patients (68 patients in the Orthopedics and Traumatology Clinic, Clinical Center in Podgorica, Montenegro, and 145 patients in the Orthopedics and Traumatology Clinic Military Medical Academy in Belgrade, Serbia) in a 24-month period, from 2006 to 2008.

A decision about the treatment of medial meniscal lesion was made according to patient factors and type of meniscal injury. In our institutions we perform various techniques of meniscal reparation but in this study we only presented series of medial meniscus injuries with partial arthroscopic meniscectomy.

Three primary methods of diagnosing medial meniscal injury were anamnesis, physical examination and magnetic resonance imaging (MRI).

Physical examination – numerous specialized tests have been described that may aid in making the diagnosis of meniscal tear. We mainly relied on joint line palpation, the flexion McMurray test, the Apley grind test.

In 58 (27.2%), cases we used general and in 155 (72.8%) regional anesthesia. Perioperative antibiotics administered were in most cases cefazolin, ceftriaxone or in the case of a documented penicillin or cephalosporin allergy gentamycin, amikacin or clindamycin. Some patients received intraarticular injection of hyaluronic acid intraoperatively.

Partial resection of the medial meniscus is advocated when other treatment modalities are not attainable. We followed Metcalfs et al. [13] general guideline for arthroscopic resection that applies to most resectable meniscal lesions: all mobile fragments that could be pulled past the inner margin of the meniscus into the center of the joint were removed, the remaining meniscal rim was smoothed to remove any sudden changes in contour that might lead to further tearing, the probe was used repeatedly to gain information about the mobility and texture of the remaining rim, we tried to protect meniscocapsular junction and the peripheral meniscal rim during resection (this maintains meniscal stability and is vital in preserving the load transmission properties of the meniscus), a perfectly smooth rim was not mandatory since a repeated arthroscopy showed rim remodeling and smoothing at 6 to 9 months. We used both manual and motorized resection instruments, in uncertain situations, more rather than less intact meniscal rim was left to avoid segmental resection, which essentially results in a total meniscectomy.

During rehabilitation full range of motion was immediately allowed, 50% weight bearing and forearm crutches were used for 2–4 days. Afterwards the patients progressed to full weight bearing according to pain tolerance and swelling. Physical therapy exercises to achieve complete range of motion and optimal muscle strength were recommended to athletes and patients with long lasting complaints (in most cases those were patients older than 40 years). We suggested to all patients to suspend sports participation for approximately three weeks.

In comparison of pre- and postoperative results, we used a 2000 IKDC subjective knee evaluation form.

## Results

All presented cases underwent partial arthroscopic medial meniscectomy (Figures 1 and 2). In the series of arthroscopicaly treated medial meniscus tears we noted 78 (36.62%) vertical complete bucket handle lesions, 19 (8.92%) vertical incomplete lesions, 18 (8,45%) longitudinal tears, 35 (16.43%) oblique tears, 18 (8.45%) complex degenerative lesion, 17 (7.98%) radial lesions and 28 (13.14%) horisontal cleavage lesions. There were 171 men (80.28%)

**Fig. 1 – Bucket handle tear and partial meniscal resection**

**Fig. 2 – Oblique tear pre- and post partial meniscectomy**

and 42 women (19.72%). Mean patient age was 36.6 years (range from 15 to 81 years).

In our study we had correlation between positive McMurray and/or Apley test and arthroscopic confirmation of medial meniscal tear in 78% of the presented cases. Joint line tenderness was positive in 86% of the patients who underwent arthroscopic meniscectomy.

Medial meniscus lesion was arthroscopicaly treated in 119 left knees and in 94 right knees. A total of 89% of presented arthroscopic meniscectomies were performed as one day surgery. A total of 51 (23.94%) of patients received intraarticular injection of hyaluronic acid following arthroscopic partial meniscectomy.

In 39 (18.30%) cases of medial meniscus lesion during arthroscopy, we found signs of a complete or partial rupture of the ACL while in 8 cases (3.75%) we noted that medial meniscus tear was accompanied with lateral meniscus tear.

Totally 175 of 213 patients underwent knee MRI previous to arthroscopy and in 6 cases medial meniscal tear was not seen on MRI. In our series of arthroscopic partial medial meniscectomy the accuracy of preoperative MRI was 96.57%.

Mean preoperative IKDC score was 49.81%, a month after arthroscopic medial meniscectomy the mean IKDC score was 84.08%, and 6 months after the mean IKDC score was 90.36%; 6 months after the procedure 197 (92.49%) patients had good or excellent subjective postoperative clinical outcomes; 14 (6.57%) patients subjectively did not notice a significant improvement after the intervention, and 2 (0.93%) patients had no subjective improvement after partial medial meniscectomy at all.

In our series we had 6 (2.81%) complications. In 2 (0.93%) cases we had knee hemartros which were resolved by puncture, 2 (0.93%) cases of instrument failure (arthroscopic knife breakage) and 2 (0.93%) patients had infection (cultures were positive for *Staph. aureus*) which was resolved by rearthroscopy and with high doses of *iv* antibiotics.

## Discussion

In the past two decades numerous advances in meniscal repair and meniscal transplantation techniques were achieved, mostly with the intention of achieving long-term delay of knee degenerative changes. In some cases, however, partial meniscectomy is still required, and is the treatment of choice [15, 16].

Medial arthroscopic partial meniscectomy in general is considered as a safe and reliable procedure. Major advantages of partial arthrocopical meniscectomy over meniscal repair include decreased hospitalization, shorter rehabilitation and a reduction in health care system costs. Numerous studies on arthroscopic partial meniscectomy reported 80% to 90% satisfactory clinical results.

Burks et al. [17] reported both clinical and radiographic results of patients with a nearly 15-year follow-up after partial meniscectomy. They reported 88% good or excellent clinical outcome and minimal degenerative radiographic changes compared with the untreated knee.

On the other side a number of studies have questioned whether partial meniscectomy is a procedure without delayed consequences. Rangger et al. [18] evaluated patients who had undergone arthroscopic partial meniscectomies at an average of 4 years and found increased radiographic changes of osteoarthritis in 38% of the patients who had undergone partial medial meniscectomy, however, they noted that these changes did not correlate with subjective postoperative results because 86% to 91% of patients had good or excellent clinical outcomes. Glatthorn et al. [19] have shown that quadriceps weakness exists 6 months after arthroscopic partial meniscectomy. However, in our series 6 months postoperatively in most cases we found quadriceps weakness only in knees with concomitant ACL deficiency. Fabricant and Jokl [20] have shown in their study that patient age and sex hawe no significant association with any clinical or radiographic outcome variables at 8.5, 12, and 15 years, that osteoarthritis progressed more after medial partial meniscectomy in patients older than 40 years than in younger patients, and that the best radiographic results in patients who underwent medial meniscectomy occurred in valgus knees compared with varus knees.

In our series a full range of motion was immediately allowed, 50% weight bearing and forearm crutches were used for 2–4 days, patients were encouraged to return to normal daily activities and sports three weeks after the intervention, and we did not note any problems during study with this rehabilitaion regime. Lubowitz et al. [21] in the study of return to activity after arthroscopy concluded that most patients had no knee-related activity restrictions 4 weeks after arthroscopy. Hempfling [22] found that intra-articular hyaluronic acid after knee arthroscopy leads to a lasting improvement in pain and functional impairment being a suitable way of achieving long-term stabilisation of the treatment outcome. We applied intra-articular injections of hyaluronic acid following arthroscopic partial medial meniscectomy in 51 cases, and found a significant reduction in pain in the first month after arthroscopy compared to the group of patients who had not underwent postarthroscopical viscossuplementation. In order to obtain aduequate assessments we used IKDC score. The IKDC is considered a reliable and valid instrument for use in a broad patient population [15]. There are also other scoring systems available, such as Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee that have demonstrated acceptable psychometric performances as outcome measures for patients with a meniscal injury of the knee [16].

Complication related to arthroscopical partial meniscectomy can be divided into those related to arthroscopy in general and those specific for partial meniscectomy. Small [23] reported on the complications of 21 arthroscopists over 19-month period and found that complication rate for medial meniscectomy was 1.78%, and that instrument failure represents 2.9% of all arthroscopic complications. We had 6 (2.81%) complications. Aside from the general complications of knee arthroscopy (hemarthrosis and infection) partial meniscectomy was in our series complicated by instrument failure in only 2 (0.93%) cases; we had none of other reported com-

plications as knee ligament or neurovascular injuries or patients with the persistent pain after partial meniscectomy.

**Conclusion**

Arthroscopic partial medial meniscetomy is minimally invasive diagnostic and therapeutic procedure.

In most cases, arthroscopic partial medial meniscetomy surgery stands as an ideal procedure for the concept of one day surgery.

Whenever the diagnosis of meniscal tear is less clear, preoperative knee MRI should be obtained, thanks to its accuracy, opportunity for errors is significantly reduced.

In well selected cases, when repair techniques are not viable option, partial medial meniscetomy is a method of choice for treatment of medial meniscus injuries. It has small rate of complications, low morbidity and fast rehabilitation. Well performed partial medial meniscectomy results in alleviation of knee pain, improvement in knee function, and good patient satisfaction.

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Received on October 18, 2010.
Accepted on January 25, 2011.

GENERAL REVIEW

UDC: 616.12-008.331.1::616-053.9
DOI:10.2298/VSP1109779I

# Arterial hypertension in the elderly

## Arterijska hipertenzija kod starih osoba

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**Key words:**
**hypertension; systole; aged; risk factors; drug therapy.**

**Ključne reči:**
**hipertenzija; sistola; stare osobe; faktori rizika; lečenje lekovima.**

### Introduction

More than half of the individuals older than 65 are affected by hypertension. Isolated systolic hypertension, characterized by an increase in systolic arterial pressure without an increase in diastolic one, is the most frequent type of hypertension in persons over 50 years of age. It occurs *de novo* or after a long period of inadequately treated systolic-diastolic arterial hypertension. The main reason for its occurence is many years mediated increase in stiffness of the large elastic arteries. This structural change is responsible for the occurrence of high systolic pressure in the following two ways: by blood ejection from the left ventricle into the stiff arterial system of decreased distensibility, and by the increase in the pulse wave velocity with the reflection wave occurring during late systole. The increased peripheral vascular resistance, sympathetic stimulation and activities of the Renin Angiotensin Aldosteron (RAA) system play a less significant role in the incidence of arterial hypertension in the elderly than is the case with individuals affected by structural and functional changes of the aorta.

Previously, vascular stiffness and an increase in systolic pulse pressure were considered as a part of the aging process and there was no insistence on treating this type of hypertension. Nowadays, when it is known that arterial hypertension in the elderly increases the risk of cardiovascular diseases three to four times more than in younger persons, it is insisted that this significant risk factor be corrected.

In addition to necessary life style modifications, the advantage in medical treatment is given to thiazide diuretics and dihydropiridines from the group of calcium channel blockers. The therapy should be always adjusted to comorbidities.

Elderly persons are defined as individuals at the age of 65 and older. They represent a growing segment of the population. In 1990, elderly persons comprised 13% of the total population of the USA and it is estimated that until 2040 they will constitute 20% of the population [1]. As regards the number of elderly persons, Serbia is ranked as the fourth country in the world, after Greece, Italy and Japan. According to the data of the Statistical Office of the Republic of Serbia, approximately 17.24% of the population was elderly at the end of the last century, and it is estimated that this number will increase to 30% as far as 2025 [2].

Similarly, the percentage of very old persons (older than 85) is constantly growing and it is assumed that there will be 16 million very old persons in the world by the middle of the 21st century [1].

More than half of the individuals over 65 years of age have hypertension [1]. The principal reason for the increased incidence of arterial hypertension in the elderly is the growing number of persons suffering from isolated systolic hypertension (ISH), which is also the most frequent type of hypertension found in this age group [3, 4]. Isolated systolic hypertension is defined as an elevated systolic blood pressure ≥ 140 mmHg with the diastolic pressure value < 90 mmHg.

Much more significant fact than the increased incidence of the elderly is the fact that the elderly with arterial hypertension, wheter it is isolated systolic or both systolic and diastolic, are at three to four times higher risk to develop cardiovascular diseases than young individuals. It is an important risk factor for stroke, heart failure, coronary artery disease, terminal renal failure and death [1].

#### *Epidemiology of arterial hypertension in the elderly*

The results of the thirty-year follow-up of patients included in the Framingham Heart Study have shown that systolic blood pressure (SBP) continually increases from the age of 30 to 84. Unlike systolic blood pressure, diastolic blood pressure (DBP) increases until the fifth decade and

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then gradually decreases through the age of 60. This results in the increase of pulse pressure (PP) [5], which is ilustrated in Figures 1 and 2.

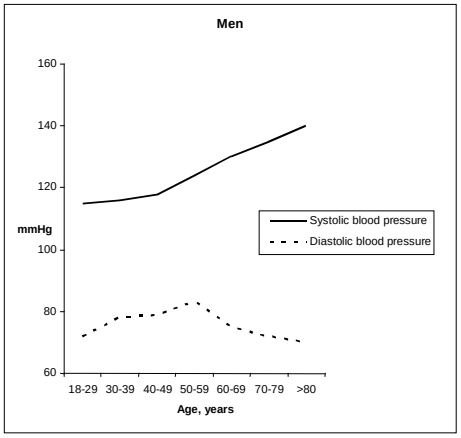


**Fig. 1 – Mean systolic and diastolic blood pressures by age for men in the US population, 18 years of age and older [5]**

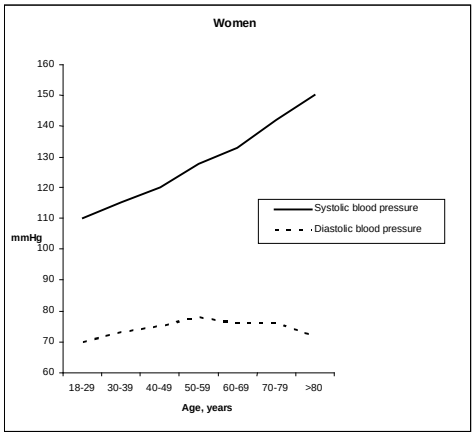


**Fig. 2 – Mean systolic and diastolic blood pressures by age for women in the US population, 18 years of age and older [5]**

As it is already mentioned ISH is the predominant type of arterial hypertension among individuals older than fifty. ISH is present in 8% to 15% of all individuals over 60 years of age [6]. The third National Health and Nutrition Examination Survey (NHANES III) has shown that more than 80% of persons over 50 who suffer from arterial hypertension have systolic hypertension (Figure 3) [7]. Its incidence progressively increases with age by 5%, 15%, and 25%, in the sixth, seventh and eighth decade, respectively [6].

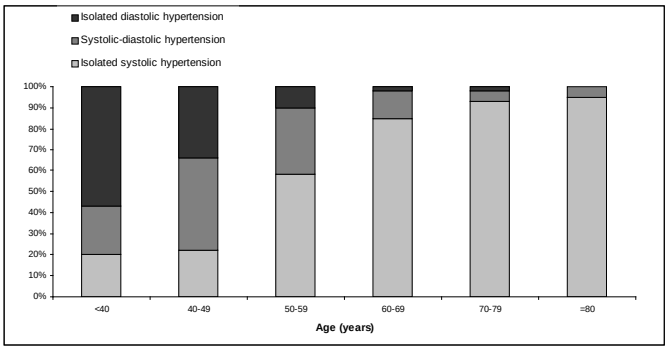


**Fig. 3 – Categories of blood pressure in untreated hypertensive patients illustrating the importance of systolic blood pressure beyond the age of 50 years**

Despite the general pattern of arterial blood pressure changes are similar for both genders, the arterial pressure, which is lower in women younger than 50, gradually increases from that age and results in values significantly higher than in men over sixty [8]. This phenomenon is a consequence of menopause, which enhances the age-induced increase of arterial blood pressure.

*Structural changes of large arteries in elderly persons and the reasons of their occurrence*

The age-associated increase in stiffness of large arteries is the main characteristic of arterial hypertension in the elderly [2]. Structural changes affect the aorta and elastic arteries, whereas the structure of muscular arteries does not change significantly. Elastic arteries undergo thickening of the tunica intima and their tunica media loses the ordered structure of elastic fibre and lamina that become thinner due to ruptures and fragmentation. Levels of collagen and matrix protein rise. Calcium binds to elastin and the undifferentiated muscle cells of the tunica media that proliferate and migrate into the intima. Proliferation of connective tissue results in the thickening of the intima and media fibrosis, along with the loss of distensibility and partial loss of its contractility.

A logical explanation for these alterations lies in the fact that the stress cycle accumulated in six decades as a result of more than two billion expansions of the aorta in the course of ventricular contraction leads to fatigue of the material and consequential structural changes [9, 10].

Genetic polymorphism also plays a role in the process of cardiovascular aging [11]. A combination of two or three polymorphisms may influence the characteristics of the vascular wall much more consistently than a single polymorphism. In elderly persons suffering from ISH, the DD genotype of angiotensin-converting enzyme gene polymorphism, combined with the specific genotype of aldosterone synthetase and α-adducin gene polymorphism influence the reduction of arterial compliance and distensibility, which in turn are responsible for the incidence of ISH and augmentation of PP.

The age-induced structural changes in large arteries occur independently of other risk factors, but the role of hypercholesterolemia, smoking, insulin resistance, etc. cannot be ignored in the development of endothelial dysfunction, and thereby the development of arterial hypertension. On the other hand, high systolic blood pressure increases wall stress that causes the damage of endothelium, which, in a vicious circle, maintains high levels of arterial blood pressure.

*Pathophysiology of arterial hypertension in elderly persons*

The value of systolic blood pressure (SBP) is a result of the interaction among the following three factors: characteristics of left ventricular ejection, and compliance of large arteries, and propagative and reflective properties of the pulse wave in the arterial tree.

As noted above, the dominant reason for the increased SBP in the elderly with ISH is an increased stiffness of the arteries, which produces negative effects in two ways – through direct and indirect mechanisms [12, 13]. The direct mechanism involves the creation of high systolic pressure by the ejection of blood from the left ventricle into the stiff arterial system of decreased distensibility. The indirect mechanism implies the influence that the arterial stiffness has on the velocity of pulse wave and on the pressure wave reflection time. With the increase of arterial stiffness and the velocity of the pulse wave, the reflection wave returns into the central artery earlier, usually during late systole and less often during early diastole. This causes increase in the aortic and left ventricular pressure during systole and a reduction aortic pressure during diastole [14]. This is shown in Figure 4.

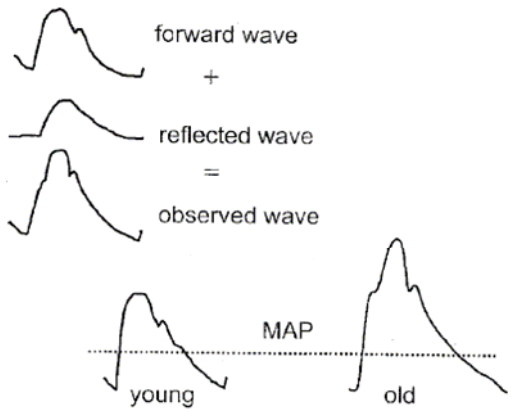


**Fig. 4 – With aging large arteries stiffen, and the reflected wave, which travels faster, is superimposed over the forward wave in early systole, increasing both systolic and pulse pressure**

In our research, published ten years ago, we found that aortic distensibility estimated by echocardiography inversely correlated with pulse wave velocity in patients with isolated systolic hypertension older than 65 [15].

One of the characteristics of arterial hypertension in the elderly is an increase in the activity of the sympathetic nervous system which leads to down-regulation of adrenergic receptors [16]. On the other hand, beta-adrenergic receptor sensitivity is diminished, which reflects in a decreased chronotropic response to beta antagonists and indicates a lesser significance of sympathetic stimulation in the development of arterial hypertension and less efficiency in treatment with beta blockers in elderly individuals.

Another mechanism contributing to the development of arterial hypertension in the elderly is endothelial dysfunction [17]. It is manifested in decreased nitric oxide-mediated dilatation. Taking the increase in aortic pulse wave velocity as the measure of stiffness of large arteries, Wallace et al. [18] have shown that it correlates with endothelial dysfunction.

Additionally, the number of nephrons decreases with age and a total of 800,000 nephrons at birth reduces by half at the age of 70 [19]. The nephrosclerosis developed as a result of aging and arterial hypertension leads to the decreased secretion of renin from the kidneys. Thus, in elderly with arterial hypertension we usually find decreased levels of renin in circulation and lower plasma renin activity. Low levels of renin can also occur as a result of the salt retention tendency with consequential volume load, which leads to increase of arterial pressure and suppression of renin release from the juxtaglomerular cells. This characteristic of the arterial hypertension in elderly persons explains better responsiveness of arterial hypertension to the application of diuretics and calcium channel blockers, and its lower responsiveness to the treatment with ACE inhibitors, AT1-receptor blockers and beta blockers.

Elderly hypertensive persons, as well as the normotensive ones, show salt sensitivity, which is indirectly proven by significant decrease of blood pressure values with the loss of salt or reduction of salt intake [13, 20].

Elderly persons who suffered from arterial hypertension at younger age and sustained it at old age show a more significant increase in peripheral vascular resistance than those whose aging was the reason for the occurrence of arterial hypertension.

Hemodynamically, ISH is characterised by a decrease in cardiac output, stroke volume and intravascular volume [10]. Baroreceptor sensitivity to changes in blood pressure levels is decreased, which results in significant variations of the arterial blood pressure values.

*Specific characteristics of arterial hypertension in the elderly*

Diagnosing arterial hypertension in the elderly, especially very old ones, may be accompanied with problems. In approximately 2% to 5% of elderly persons with rigid, calcified arteries, it is impossible to ensure the collapse of the brachial artery, which gives false high values of the arterial blood pressure [21]. This phenomenon is called pseudohypertension. Pseudohypertension is suspected in persons with minimal vascular damage of the retina in spite of the high measured values of arterial blood pressure, and in those who show postural symptoms after discontinuation of therapy.

Arterial hypertension in the elderly is characterised by significant oscillations in the values of arterial pressure

which can be proved by 24-hour ambulatory blood pressure monitoring. In one of our researches we found that variations of systolic pressure values in hypertensive subjects older than 60 years correlated with their age and they were the most frequent in patients older than 80 years of age. We also determined that reduction of systolic blood pressure during night inversely correlated with age [22]. However, significant individual variations of systolic arterial pressure in elderly persons during the night indicate the risk of brain stroke. The risk of cardiovascular events is also increased during the early morning increase in the values of arterial pressure [13]. The white coat hypertension was detected in 24% of elderly persons. In one of our investigations we found that the prevalence of the white coat hypertension was higher in the elderly with isolated systolic hypertension than in patients with combined systolic and diastolic hypertension which were the same age [23]. Another phenomenon that may be seen in the elderly is the phenomenon of reverse white coat hypertension, which implies that the values obtained during 24-hour monitoring of arterial pressure are higher than those obtained through conventional measuring in the doctor's office.

Moreover, another phenomenon characteristic of the elderly population is ortostatic hypotension, which is defined as a fall in SAP by at least 20 mmHg and a fall in diastolic pressure by 10 mmHg within three minutes after getting up. The main reasons for its occurrence are the decrease in baroreceptor sensitivity and the deficit of heart-rate response to the change in body position. The incidence of occurrence of ortostatic hypotension increases from 17% in persons 65 to 74 years of age to 26% in persons older than 85. Ortostatic hypotension poses the risk of traumatism, and, on the other hand, it is a risk factor for cardiovascular diseases. Likewise, ortostatic hypotension increases the risk of brain stroke and dementia [24].

Reduction of arterial blood pressure may also occur after eating, which is referred to as postprandial hypotension [13]. The basic reason for its occurrence is an inadequate response to vasodilatory effects of gastrointestinal peptides and insulin. It has been established that approximately 70% of individuals older than 70 show fall in arterial pressure values after meals, and that in 24% of the cases reduction is over 16 mmHg for systolic and over 12 mmHg for diastolic arterial pressure. Not a small number of the elderly have a weakness, even syncope after breakfast which, besides all the possible metabolic reasons, can be also explained with the postprandial hypotension that is easily detected by the 24-hour blood pressure monitoring. However, if the evidence of postprandial hypotension is missing then the 24-hour blood pressure monitoring should be repeated at least twice if there are no conditions for hospitalization.

*The implications of high pulse pressure*

This caracteristics of arterial hypertension in the elderly complicate the treatment of these patients. Yet, they cannot be a barrier to the medical treatment, which is extremely important due to the subclinical and clinical consequences of arterial hypertension in elderly persons. The left ventricle becomes stiff, in addition to the stiffness of the large arteries [12]. Moreover, left ventricle hypertrophy is often found in the elderly suffering from ISH. In our examination of the influence of the aortic distensibility on systolic and pulse pressure in patients with isolated systolic hypertension, we found that the patients with this form of arterial hypertension in addition to impaired left ventricular relaxation also have concentric remodeling pattern of left ventricle as dominant pattern [15]. Stiffness of the left ventricle combined with decreased distensibility of the arterial system increases the risk of cardiovascular diseases in several ways. Among other problems, the wall stress increases, which in turn enlarges the energy necessary for cardiac cicle. The increase in left ventricular stress during late systole leads to incomplete diastolic relaxation, and eventually to heart failure with preserved ejection fraction.

Isolated systolic hypertension is often combined with coronary artery disease, thrombotic and hemorrhagic strokes, dementia, peripheral arterial disease and slow progressing heart and renal failure [25]. Comparing the results of normotensive elderly persons with the elderly suffering from ISH it has been shown that the increase of systolic blood pressure by 1 mmHg raises the incidence of coronary artery disease, stroke and overall mortality by 1%. This finding is real evidence for the significance and severity of this type of arterial hypertension.

*Treatment of arterial hypertension in the elderly*

The purpose of treating arterial hypertension in elderly persons is identical to the purpose of treating it in young and middle-aged populations – its reduction to values below 140/90 mmHg, *ie* reduction to values below 130/80 mmHg in the high-risk patients with clinical damage (after acute myocardial infarction, due to renal failure, after cerebrovascular insult) and those suffering from diabetes mellitus [26]. Like in the case with hypertensive patients in younger age, reduction of body weight, restriction of salt intake according to DASH (Dietary Approaches to Stop Hypertension), increased physical activity and moderate alcohol intake (one serving per day for women and two servings for men) is advised for the elderly regardless of the type of arterial hypertension [24].

According to our experience an essential precondition to achieve the target values of arterial blood pressure in patients older than 65, and especially older than 70 years of age, is the reduction in salt intake of 100 mmoL/day (*ie* 4.7 to 5.8 g NaCl). This can be explained by the abovementioned salt sensitivity which increases through the lifetime. One of the problems in the modification of a lifestyle is the changes in the bones and joints, which restrict mobility and require a combined medical approach including physiotherapist who will show these patients some exercises that are crucial for maintaining and prevention of the reduction of large arteries distensibility as well as for the sustenance of a desired weight and the decline of body overweight.

In drug treatment, there are five available large groups of antihypertensives: thiazide diuretics, calcium channel blockers, angiotensin–converting enzyme (ACE) inhibitors,

angiotensin (AT)1-receptor blockers, and beta blockers. Each of these groups reduces the values of arterial blood pressure in a similar way, thus reducing the incidence of cardiovascular events. Different clinical trials have shown that medicament treatment of these patients reduced the risk of cerebrovascular insult, coronary artery disease, acute myocardial infarction, mortality of coronary artery disease and total mortality (Tables 1 and 2). The specificity of treating elderly persons is in introducing smaller dosage of the drugs due to the significant occurrence of adverse effects in this population.

ceptor blockers) in relation to the "old" (beta blockers and thiazide diuretics) antihypertensives. The ALLHAT study showed that thiazide diuretic, ACE inhibitor and calcium channel blocker reduced the frequency of cardiovascular events in the subgroup of patients older than 65 years of age equally well [34]. The LIFE study showed that the AT1 receptor blocker was more effective than beta blocker in the prevention of cardiovascular events, especially cerebrovascular insult in hypertensive patients aged 55 to 80 with left ventricle hypertrophy [35]. The advantage of AT1 receptor blockers

**Table 1**

**Clinical trials of different antihypertensive drugs in the elderly**

| Clinical trial | Population | Treatment |
|---|---|---|
| STOP-Hyper [27] | Age, 70–84 years<br>SBP ≥ 180 mmHg and/or<br>DBP ≥ 105 mmHg | Metoprolol/ atenolol/ pindolol or hydrochlorthiazide/amiloride *vs* placebo |
| SHEP [32] | Age ≥ 60 years<br>SBP ≥ 160 mmHg and<br>DBP < 90 mmHg | Chlorthalidone or amiloride *vs* placebo |
| Syst-Eur [33] | Age ≥ 60 years<br>SBP ≥ 160 mmHg and<br>DBP < 95 mmHg | Nitrendipine, enalapril and hydrochlorthiazide *vs* placebo |
| MRC [28] | Age, 65–74 years<br>SBP ≥ 160 mmHg | Amiloride + hydrochlorthiazide or atenolol *vs* placebo |
| HYVET [37] | Age ≥ 80 years<br>SBP ≥ 160 mmHg<br>and<br>DBP > 90 mmHg | Indapamide SR + perindopril *vs* placebo |
| LIFE [35] | Mean age 67<br>Hypertension with LVH | Losartan *vs* atenolol |

**Stop-Hyper – Swedish Trial in Old Patients with Hypertension; SHEP – Systolic Hypertension in the Elderly Program; Syst-Eur – Systolic Hypertension-Europe; MRC – Medical Research Council trial of treatment of hypertension in older adults; HYVET – Hypertension in the Very Elderly Trial; LIFE – Losartan Intervention for Endpoint reduction in hypertension; SBP – systolic blood pressure; DBP – diastolic blood pressure; LVH – left ventricle hypertrophy**

**Table 2**

**The most important outcomes of clinical trials**

| Trial | Stroke | CAD | AIM | CAD mortality | Total mortality |
|---|---|---|---|---|---|
| STOP-Hyper | -47% | -13% | -40% | NS | -43% |
| SHEP | -36% | -27% | -32% | -20% | -13% |
| Syst-Eur | -42% | -26% | -31% | -27% | -14% |
| MRC | -25% | -19% | -17% | -9% | -3% |
| HYVET | -30% | / | / | -23% | -21% |
| LIFE | -40% | / | -11% | -46% | -28% |

**Stop-Hyper – Swedish Trial in Old Patients with Hypertension; SHEP – Systolic Hypertension in the Elderly Program; Syst-Eur – Systolic Hypertension-Europe; MRC – Medical Research Council trial of treatment of hypertension in older adults; HYVET – Hypertension in the Very Elderly Trial; LIFE – Losartan Intervention for Endpoint reduction in hypertension; CAD – coronary artery disease; AIM – acute myocardial infarction; NS – statistically non-significant; / – not determinated**

The initial randomized controlled studies showed the benefit from the use of diuretics or beta blockers compared with placebo in the treatment of various forms of arterial hypertension in the elderly [27–30]. However, Masserli et al. [31] using meta-analysis showed that beta blockers used in the treatment of arterial hypertension in the elderly were less effective than diuretics in the prevention of cardiovascular events. Based on the results of large randomized studies (SHEP and Syst-Eur) thiazide diuretics and calcium channel blockers (especially dihydropiridines) were suggested as the first-line therapy in the treatment of ISH [32, 33]. The studies that followed examined the advantage of the "new" (new generation dihydropiridines, ACE inhibitors and AT1 receptor blockers) in relation to the "old" (beta blockers and thiazide diuretics) antihypertensives. The ALLHAT study showed that thiazide diuretic, ACE inhibitor and calcium channel blocker reduced the frequency of cardiovascular events in the subgroup of patients older than 65 years of age equally well [34]. The LIFE study showed that the AT1 receptor blocker was more effective than beta blocker in the prevention of cardiovascular events, especially cerebrovascular insult in hypertensive patients aged 55 to 80 with left ventricle hypertrophy [35]. The advantage of AT1 receptor blockers in the prevention of the nonfatal cerebral stroke in patients older than 70 years of age with ISH was confirmed by the results of SCOPE study [36].

Last year the results of the HYVET study which demonstrated the benefit of treatment of very old hypertensive patients (older than 80) were published. It was shown that the use of indapamide with or without perindopril in this population of patients led to a reduction of death counts from cerebral stroke, heart failure and total mortality. This eliminated the suspicion about necessity of treatment of very old hypertensive patients [37].

As it can be concluded from the above-mentioned, the large randomized studies have shown the benefit from the

applying of all groups of antihypertensives in treatment of old hypertensive patients. However, in everyday practice we face the dilemma about which medication to use first. The basic thing in these circumstances is the information about the associated risk factors and the information about subclinical and clinical manifestations of target organs damage. Undoubtedly, in patients with ISH without associated risk factors and organs damage we will apply thiazide diuretics with or without calcium channel blockers (Table 3). In other conditions, when elderly patients have associated diabetes mellitus or heart failure, and after acute myocardial infarction ACE inhibitors or AT1 receptor blockers have priority, as well as in younger or middle-aged patients. In older hypertensive subjects with proved coronary artery disease beta blocker will be applied regardless the results of study which showed a little benefit from their usage in the prevention of cardiovascular events (not only because of well-known advantages of this class of drugs in the coronary heart disease but also because the study included only patients without coexisting coronary heart disease). Similarly, in the old hypertensive patients with vascular hypertrophy (changes in intima-media thickness of carotid artery) we should try to regulate arterial hypertension using metabolic neutral drugs with antiatherogenic potential (ACE inhibitors, AT1 receptors blockers or calcium channel blockers). It means that the decision about antihypertensives we will prescribe in the elderly depends on a comprehensive assessment of each patient individually.

One of the problems in the treatment of arterial hypertension in the elderly is that the majority of patients with ISH have difficulty to achieve and maintain the reduction of arterial blood pressure to the target value using monotherapy, because a combined therapy is required. In these situations we apply the same principles of drug selection as previously mentioned. Nevertheless, a number of patients apart from taking three antihypertensives (thiazide diuretic is one of them) do not have optimal regulation of arterial pressure. If arterial hypertension exists in spite of compliance of proposed lifestyle changes and advised polytherapy, after excluding secondary forms of arterial hypertension (stenosis of renal artery usually of atherosclerotic nature), we can conclude that it is a resistant arterial hypertension in question. The reason for resistant arterial hypertension in the elderly are the structural changes of large arterial blood vessels. In these circumstances, we use different modifications of a medical treatment to achieve a regular blood pressure, which is sometimes impossible.

**Table 3**

**Recommendations for arterial hypertension treatment in the elderly**

- The aim of the treatment of arterial hypertension in the elderly is the reduction of systolic pressure values to less than 140 mmHg, diastolic pressure below 90mmHg and in patients with ISH the value of systolic pressure < 140 mmHg;
- In order to achieve the blood pressure regulation it is necessary to modify the lifestyle, firstly to reduce salt intake and body weight in obese patients, then to stop smoking and reduce alcohol intake;
- In medicament treatment we should start with a half of the usual dose because of a significant manifestation of adverse effects in this group of patients;
- In patients with ISH without associated risk factors and target organs damage the advantage is given to thiazide diuretics and calcium channel blockers;
- In all other circumstances (which are to appear far more often in everyday practice) the choice of medications should be adjusted in accordance with associated risk factors and clinical and subclinical target organs damage.

**ISH – isolated systolic hypertension**

Additionally, there is one more problem in treatment of the elderly. Namely, it is difficult to maintain optimal values of diastolic arterial pressure in these subjects with ISH. Protegerou et al. [38] have shown that the values of diastolic pressure ≤ 60 mmHg reduce survival despite of the stiffness of large arteries and the function of the left ventricle [38]. They have suggested that it requires optimization of therapy not only regarding the values of systolic, but also diastolic arterial pressure.

In these circumstances where we have a significant reduction of diastolic pressure value (≤ 60 mmHg) in patients with ISH we are satisfied with accomplished but not optimal regulation of systolic blood pressure, like in the resistant arterial hypertension.

## Conclusion

From all the abovementioned we can conclude that there is no dilemma whether the treatment of arterial hypertension of the elderly is necessary. Furthermore, it should be adapted to each patient and the success of the treatment is not always guaranteed.

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Received on March 24, 2010.
Accepted on April 15, 2011.

A K T U E L N A T E M A

613.2:612.39]:[575:61
DOI:10.2298/VSP1109786S

# Nutrigenomika – nauka za 21. vek

## Nutrigenomics – the science of the 21st Century

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**Ključne reči:**
**nutrigenomika; hrana; genom.**

**Key words:**
**nutrigenomics; food; genome.**

### Uvod

„Lekar u budućnosti više neće tretirati bolesti lekovima, već će lečiti i prevenirati bolest ishranom" (Tomas Edison).

Ishrana igra izuzetno značajnu ulogu u očuvanju zdravlja i poboljšanju kvaliteta života. Nakon dekodiranja ljudskog genoma u sklopu „*Humane Genome Project"* 2003. godine, došlo se na ideju da se strategija ishrane može obogatiti podacima o tome koji nutrijenti odgovaraju specifičnom profilu genoma [1]. Nutrigenomika je nauka koja istražuje način na koji pojedini sastojci namirnica ili njihovi metaboliti interreaguju sa genomom u cilju regulisanja strukture ili ekspresije gena, koji će posledično modifikovati ili zaustaviti progresiju bolesti [2]. Istraživanja u ovoj oblasti započeta su nakon završetka projekta aprila 2003. godine, tako da je nutrigenomika još uvek nauka u povoju.

Promene u strukturi gena nalik izolovanim nukleotidnim polimorfizmima (*single nucleotide polymoprhisms* – SNP), delecijama i insercijama mogu imati za posledicu nastanak oboljenja. Ovakve promene leže i u osnovi hroničnih bolesti i smatra se da su, i pored činjenice da su hronične bolesti izazvane brojnim faktorima, alteracije u genima glavni okidač kao i razlog za te bolesti da traju do kraja života.

Pristup nutrigenomike nam obezbeđuje da ustanovimo koji su geni aktivni, na koji način su geni/proteini povezani sa simptomima bolesti, kao i da sagledamo uticaj nutrijenata na ekspresiju gena, a samim tim i na transkripciju proteina. Trenutno se širom sveta vrše istraživanja koja bi otkrila koji nutrijenti utiču na nastanak pojedinih oboljenja, a čijom bi prevencijom bio poboljšan kvalitet života i smanjen pritisak na zdravstvene službe. Istraživanja se mogu sprovoditi u dva pravca: posmatranje efekata nutrijenata na regulaciju genske ekspresije (nutrigenomika) ili analiza značaja varijacije u genskoj strukturi u odgovoru organizma na nutrijente u ishrani (nutrigenetika). Za ovakva istraživanja od ključnog značaja su kliničke i epidemiološke studije koje mogu dati informaciju o dugoročnim posledicama ishrane na velikom broju stanovnika.

Medicinski Institut u Vašingtonu je 2006. godine zaključio da u nutrigenomici postoje tri naučna domena: nutritivna genetika (kojom identifikacija, klasifikacija i karakterizacija varijacija u humanom genomu omogućava razumevanje metabolizma i tolerancije na komponente ishrane), nutritivna epigenetika (koja se odnosi na efekte nutrijenata na DNK, čije oštećenje može proizvesti multigeneracijske efekte) i nutritivno inženjerstvo (koje koristi saznanja nutrigenomike u cilju namernog modifikovanja gena u organizmu sa ciljem poboljšanja nutritivnog stanja organizma) [3]. Razvojem svake od ovih grana doći će se do stadijuma kada će biti moguće prevenirati, modifikovati ili čak izlečiti hronične bolesti ukoliko se na bazi genetske osnove subjekta, nutritivnog statusa i nutritivnih potreba odredi odgovarajuća ishrana [2–4]. Preporuke za ishranu bi bile individualne za svakog bolesnika i imale bi za cilj prevenciju oboljenja, poboljšanje načina života i vitalnu starost [5]. Pravi značaj nutrigenomike će se pokazati nakon njenog multidisciplinatrnog razvoja. Njeno korišćenje će biti moguće u praksi nakon adekvatne obuke lekara o značaju ove grane nauke za zdravlje stanovništva i prevenciju hroničnih bolesti [3, 4].

### Metode u nutrigenomici

Nutigenomika se bazira na naukama kao što su genotipizacija, transkriptomika, proteomika i metabolomika tako da zahteva primenu velikog broja metodologija i tehnika. Genetska osnova bolesti se vrlo često ne krije u alteraciji jednog gena već je posledica kombinacije velikog broja alteracija tako da se istraživanja moraju sprovoditi modernim tehnikama koje omogućavaju istovremenu identifikaciju i do 500 000 SNP po individui. Ovakve analize zahtevaju tehnologije sekvencionih analiza i hibridizacije, a proteini i metaboliti zahtevaju različite tehnike u zavisnosti od vrste proteina i njegove hemijske prirode [6].

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Polaznu osnovu za istraživanje u oblasti nutrigenomike obično predstavlja analiza navika u ishrani ciljne populacije ispitanika. Obično se u tako opsežnim studijama koriste upitnici za ishranu koje ispitanici samostalno popunjavaju, a koje su opisali Baghurst i Record [7] jer su se pokazali efikasnim u praksi i daju tačne rezultate nakon poređenja sa laboratorijskim analizama. Upitnik sadrži listu od 4 180 uobičajenih namirnica i pitanja koja se tiču pripreme hrane i navika u ishrani [8].

Metoda ćelijske kulture pruža mogućnost izučavanja uticaja nutrijenta na razvoj različitih sojeva ćelija u kulturi. Najznačajniji test koji se sprovodi u ćelijskoj kulturi je test mikronukleus u kome se ćelije tretiraju agensom, a zatim se specifičnim bojenjem vizuelizuju elementi ćelije, a naročito jedro, u cilju otkrivanja mikronukleusa koji predstavljaju rezidue oštećenja hromozoma [5, 8]. Napredne metode kao što su *polymerase chain reaction* (PCR), *reverse transcription polymerase chain reaction* (rtPCR), *fluorescent in situ hibridisation* (FISH), *spectrol karyotyping* (SKY), *western*, *northern* i *southern blot* analiza omogućavaju uvid u mutacije gena i promene u ekspresiji gena. Naravno, ove metode će, pored uloge u eksperimentima koju danas imaju, u budućnosti biti osnovne metode za dijagnostiku i praćenje učinka odgovarajućeg režima ishrane. Metabolomika i metode kao što su high performance liquid chomatography (HPLC) i spektrofotometrija otkrivaju metabolite koji su prisutni u ćeliji ili u telesnim tečnostima sa ciljem određivanja saturacije organizma pojedinim nutrijentima.

*In vivo* istraživanja nude mogućnost određivanja efekta ishrane na različite modele bolesti, dok su klinička istraživanja još uvek retka pojava.

**Funkcionalna ishrana**

Ishrana čini značajan faktor sredine koji utiče na zdravlje, tako da nepravilna i neadekvatna ishrana nesumnjivo dovodi do promena u organizmu sa mogućim posledičnim oboljenjima. Neka od oboljenja zahtevaju skupe dijagnostičke procedure i terapiju. Ljudski organizam je adaptiran na svoju sredinu što uključuje i način ishrane kao i spektar nutrijenata koji odgovaraju njegovom genetskom sklopu. U toku adaptacije organizam se prilagođava na taj način što povećava ekspresiju proteina koji učestvuju u metaboličkom putu nutrijenata dostupnih u okruženju u kome se nalazi. Zadatak nutrigenomike je upravo otkrivanje načina aktiviranja gena, modifikacija metaboličkog puta i modifikacija ishrane [2].

Zasluga nutrigenomike je podizanje svesti o uticaju ishrane na nastanak hroničnih oboljenja sa izuzetno visokom incidencijom u čitavom svetu. Rezultat edukacije i istraživanja je koncept „funkcionalne ishrane" koji označava ishranu koja je raznovrsna i sadrži pored tradicionalnih nutrijenata i one koji imaju protektivni efekat na zdravlje. Ona se uglavnom bazira na antioksidansima, bioaktivnim peptidima, probiotskim bakterijama, visokoapsorbantnim kalcijumom, konjugovanom linolinskom kiselinom itd [5].

Do sada je dokazan uticaj pojedinih nutrijenata koji mogu usloviti pojavu bolesti kao što su: tumor dojke, tumor prostate, infarkt miokarda, dijabetes melitus, osteoporoza, reumatoidni artritis, neka neurološka oboljenja, itd. Funkcionalna ishrana teži da pažljivim odabirom nutrijenata utiče na nastanak i razvoj ovih bolesti i sa te tačke gledišta bliža je farmaceutskim preparatima nego hrani. Na taj način dolazimo do zaključka da su koncept nutrigenomike, strategije istraživanja i klinička primena slični i da se preklapaju sa onima u farmakogenomici. Veruje se da će se u budućnosti ove dve nauke uspešno kombinovati u cilju terapije teških bolesti [9].

Trenutno se nalaze u prodaji proizvodi koji snižavaju holesterol, mleko bez laktoze i probiotski jogurti. Upravo zbog toga što se ovakvi proizvodi u prodaji nalaze zajedno sa tradicionalnim proizvodima postavlja se pitanje etičnosti, jer su dostupni široj populaciji i postoji šansa da ne odgovaraju svim kupcima. Dovodi se u pitanje i etičnost reklama koje nisu dovoljno informativne i imaju za cilj zaradu. Nastavak istraživanja i dalja promocija trenda uvođenja funkcionalne hrane u ishranu opšte populacije zahtevaće zakonsku regulativu koja će obezbediti da se ciljevi ovakve ishrane kreću u željenom smeru. Pored ispitivanja bezbednosti i kvaliteta hrane, potrebno je sprovesti istraživanja koja će ispitati uticaj takvih proizvoda na organizam kao i potencijalne nuspojave pre puštanja u promet. Međutim, postavlja se pitanje da li to podrazumeva obavezu da potrošač pročita i strogo se pridržava uputstva za pripremu i korišćenje funkcionalne hrane pre svakog obroka, da se konsultuje sa lekarom pre planiranja kupovine proizvoda, kao i gde je granica između koristi i zloupotrebe [10, 11].

**Primena nutrigenomike**

Nutrijenti utiču na različite načine na strukturu gena i trenutno se vrše istraživanja o uticaju različitih nutrijenata na zdravlje. Glavni cilj istraživanja je da se nađe način da se na osnovu genetskog profila predvidi i spreči nastanak hroničnih bolesti.

Neki vitamini (kao što su tokoferol i biotin), minerali (kao što je cink) i bioaktivne supstance prisutne u hrani (kao što su kahektini i flavoni), dokazano utiču na strukturu i ekspresiju gena. Suficit vitamina D dokazano utiče na izmenu stabilnosti mRNK. Najnovija istraživanja pokazuju da unos gvožđa u količini većoj ili jednakoj 15 mg dnevno smanjuje incidenciju poremećaja DNK molekula kod mladih osoba [12]. Fenech i sar. [8] dokazali su u opsežnom istraživanju 2005. godine sprovedenom na zdravim osobama da nutrijenti prisutni u optimalnim koncentracijama, kao što su vitamin B12, folat, niacin, vitamin E, retinol i kalcijum smanjuju incidenciju oštećenja DNK molekula, dok suficit riboflavina, pantotenske kiseline i biotina povećavaju incidenciju oštećenja DNK molekula i to čak u istom nivou kao što to čine neki genotoksični i karcinogeni hemijski agensi [5, 6, 8]. Još neki od kancerogenih sastojaka hrane su: aflatoksin B1, fumonizin B1, zeralenon, ohratoksin (pronađen čak i u humanom mleku), organohlorni preparati prisutni u mesu, ribi, siru, ulju), aditivi u hrani, itd [9]. Alkohol se, takođe, pokazao kao faktor rizika od pojedinih karcinoma, što predstavlja zabrinjavajući podatak ukoliko se uzme u obzir količina unosa u opštoj populaciji [9, 13].

Jedan od agenasa koji je poslednjih godina veoma zainteresovao naučnike je resveratrol, fitoaleksin, ligand za transkripcione faktore koji direktno utiče na gensku ekspresiju. Vršena su *in vitro* ispitivanja na ćelijama androgensenzitivnim humanim ćelijama adenokarcinoma prostate (LNCaP) u kojima je dokazan njegov inhibitorni uticaj na rast malignih ćelija. Daljim ispitivanjem se pokazalo da je inhibicija nastala u transkripciji svih gena koji su pod kontrolom androgena. Pored mišljenja da se resveratrol može koristiti u prevenciji tumora prostate, na osnovu *in vivo* istraživanja na životinjama, smatra se da on ima protektivni uticaj na kardiovaskularne funkcije, da smanjuje nivo šećera u krvi i da ima antiinflamacijski efekat. Resveratrol se može naći u grožđu, borovnicama, kikirikiju i crnom vinu [14].

Esencijalni nutrijent rastvorljiv u vodi, holin, utiče na puteve transdukcije i strukturu hromatina i na taj način indirektno utiče na gensku ekspresiju. Deficit holina može imati uticaja na nastanak oboljenja jetre, ateroskleroze i nekih neuroloških poremećaja, dok suficit može imati udela u nastanku adenoma kolona. Neke od ovih tvrdnji su potvrđene u praksi na slučaju bolesnika koji su imali nizak unos holina, što je za posledicu imalo masnu jetru, opterećenje jetre i mišića, dok neki od bolesnika nisu imali posledica. Takođe, dokazana je veća predispozicija za razvoj deficita holina i posledičnih simptoma u slučaju žena sa veoma čestim SNP (mesto polimorfizma – MTHFD1-G1958A), kao i veća šansa da njihovo potomstvo ima defekt neuralne tube. Holin se može naći u namirnicama kao što su: grejpfrut, pasulj, riba, pileće meso, bademi, kikiriki, itd [15, 16].

Jedan od gena koji se najviše istražuje u nutrigenomici jeste gen koji kodira enzim metilentetrahidrofolat reduktazu (MTHFR), uključen u metabolički put kojim folati dovode do smanjenja količine homocisteina u odnosu na količinu metionina. Posledica toga je smanjenje sklonosti ka trombogenezi. Postoje dve varijante gena koje snižavaju kinetiku MTHFR. Na taj način se dolazi do zaključka da se reaktivnost MTHFR gena kontroliše zavisno od količine dva esencijalna nutrijenta: folata koji predstavlja supstrat za MTHFR i riboflavina koji predstavlja kofaktor MTHRF [6, 17].

Folati i folna kiselina mogu se naći u namirnicama kao što su spanać, jetra, suncokretovo seme, špargla, pasulj, kukuruzne pahuljice, itd. Folna kiselina koja se prirodno nalazi u hrani osetljiva je na visoku temperaturu i UV zračenje i rastvorljiva u vodi. Poremećaji u unosu folata mogu dovesti do oboljenja srca, poremećaja u reprodukciji, gojaznosti, tumora, depresije, infektivnih bolesti, itd. *In vitro* i *in vivo* studije pokazale su da deficijencija folata izaziva ekspresiju fragilnih mesta na hromozomu, prekide u hromozomima, višak uracila u DNK, mikronukleusne formacije i hipometilaciju DNK. Fenech i sar. [8] dokazali su 2005. godine da je deficijencija folata odgovorna za povećani rizik od tumora dojke. Dokazano je i da blaga deficijencija folata ima jače efekte na nestabilnost hromozoma od mutacija na BRCA1 i BRCA2 genima koji su specifični za tumor dojke [18].

Intervencije na bolesnicima pokazale su da su mikronukleusne formacije smanjene na minimum nakon unosa više od 200–400 mikrograma folne kiseline dnevno i više od 2 mikrograma vitamina B12 dnevno. Pokazalo se da je unos ovih nutrijenata bio važniji kod ljudi sa sniženim procentom apsorbcije i metabolizma ovih vitamina, čemu je uzrok uglavnom starenje [19].

Folna kiselina utiče na metilaciju DNK molekula, tako da je dokazana povećana incidencija karcinoma u populaciji kod koje je smanjen njen unos. Klinička istraživanja daju različite rezultate. Dokazano je da folna kiselina smanjuje rekurentni kolorektalni tumor, dok je u drugoj studiji dokazano da multivitaminski preparati, vitamin C, vitamin E kao i folna kiselina nemaju uticaj na smanjenje incidencije tumora pluća, sem minimalnog smanjenja incidencije pri korišćenju vitamina E [20]. U skorijim studijama se postavlja pitanje da li folna kiselina povećava rizik od poremećaja kognitivnih funkcija i pojave kolorektalnog karcinoma [21–23].

Politika američke vlade iz 1996. godine, kojom je dozvoljeno obogaćivanje proizvoda od žitarica folnom kiselinom, kao i preporučen unos od 400 mikrograma folne kiseline dnevno trudnicama sa genetskim opterećenjem (koje nosi rizik od defekta neuralne tube pre začeća i tokom rane trudnoće) dala je dobre rezultate. Etiologija ove bolesti leži u još uvek nedovoljno razjašnjenim genetskim defektima i poremećajima u metaboličkom putu [24]. Dokazano je i da unošenje folata smanjuje incidenciju spontanog abortusa [21].

Od ranije je poznat uticaj nutrijenata kao što su vitamini E4, D5 i B6 na rast ćelija tumora dojke *in vitro* čime je dokazan veliki uticaj ishrane na nastanak i razvoj ove bolesti. Takodje, dokazano je da povećan unos ribljeg ulja ima protektivan efekat kada je u pitanju razvoj tumora dojke. Najbolji dokaz je porast incidencije tumora dojke u populaciji žena u Japanu poslednjih 40 godina nakon što se u ishrani evidentno smanjio unos ribe i povećao unos biljnih ulja bogatih polinezasićenim masnim kiselinama [25]. Takodje, primećena je povećana incidencija tumora dojke u populaciji Eskima sa Aljaske u poslednjih 20 godina, što je posledica uvođenja drugačije ishrane sa većom količinom polinezasićenih masnih kiselina [26].

Pored genetske predispozicije veruje se da je ishrana jedan od važnih faktora koji mogu aktivirati ove gene ili ih održati u „tihom" stanju. Trenutno se vrše istraživanja sa ciljem otkrivanja nutrijenata i načina njihovog uticaja na ćelije. Na animalnim modelima je dokazan uticaj polinezasićenih masnih kiselina (PMK) na nastanak, progresiju i metastazu tumora dojke. Polinezasićene masne kiseline, kako je dokazano u skorijim studijama, utiču na aktivnost receptora epidermalnog faktora rasta koji je uključen u regulaciju onkogena kao što su c-myc, c-fos, neu/c-erb-b2 koji utiču na progresiju tumora [27]. Kod miševa je dokazano da paralelan unos PMK i koenzima Q10 produžava životni vek, što nas vraća na antioksidante i njihov uticaj na genetsku osnovu bolesti. Pokazalo se tačnim da koenzim Q 10 ima protektivan uticaj ne samo na tumor dojke već i kada su u pitanju mnoge bolesti starenja, jer potencijalno deluje na očuvanje integriteta dvolančane DNK [28].

Dokazano je da izvesni nutrijenti imaju protektivni efekat kada je u pitsnju nastanak oboljenja oka izazvanih starenjem (makularna degeneracija i katarakta). Zbog stalne izloženosti oka zracima sunca ono je osetljivo na oksidativni stres što za posledicu ima alteracije u genomu i promene na

oku. Takođe, evidentno je da se ova oboljenja javljaju u porodicama, kao i među blizancima. Antioksidanti kao što su vitamin C, vitamin E (seme suncokreta, orasi, bademi, lešnici, spanać, paradajz, itd.) i cink (semenke različitih vrsta i žitarice) imaju protektivan efekat u oba slučaja. Takođe, karotenoidi mogu delovati protektivno jer se oni akumuliraju u retini, gde nakon formiranja makularnog pigmenta, kao i nakon gomilanja u sočivu, prave sloj filtera za plavi spektar svetlosti. Dokozaheksaenoična kiselina (polinezasićena masna kiselina) izuzetno je važna za očuvanje retine [29].

Hughes-Fulford i sar. [30] dokazali su da linoleinska i arahnoidonska masna kiselina izazivaju povećani rast ćelija tumora prostate PC-3, dok oleinska kiselina i eikozapentenoična kiselina smanjuju njegov rast. Daljim istraživanjem je pronađeno da dodatak arahnoidonske kiseline izaziva istovremeni porast transkripcije c-fos gena koji utiče na propagaciju rasta ćelija. Eikozapentanoična kiselina (EPA) koja pripada omega-3 polinezasićenim masnim kiselinama kao prirodni sastojak ribljeg ulja smanjuje inflamaciju u *in vitro* i *in vivo* uslovima. Ovakav nalaz se može primeniti u lečenju i prevenciji bolesti kao što je osteoartritis jer je EPA izuzetno uspešna u redukovanju ekspresije gena u hondrocitima koji kodiraju enzime čija je funkcija degradacija hrskavice [31].

Uz pomoć *Dietary Approaches to Stop Hypertension* (DASH) režima ishrane postignuti su mali koraci u borbi protiv hipertenzije, međutim, u studijama koje su uzele u obzir dugoročni učinak ovakve ishrane pokazalo se da se moraju pronaći efektivniji režimi ishrane za dugoročnu redukciju krvnog pritiska [32]. Pretpostavlja se da odgovor leži u tome što DASH režim ishrane utiče primarno na osobe sa AA genotipom za angiotenzinogen, dok je manje efektivna kod osoba sa GG genotipom. Varijanta gena (AA varijanta) za angiotenzinogen kodira cirkulišući ANG protein koji zatim utiče na povećanje krvnog pritiska [33, 34].

Nutrigenomika nudi rešenje za kardiovaskularna oboljenja i preko modifikacije metabolizma Apo-A1 lipoproteina koji igra centralnu ulogu u nastanku i razvoju koronarnog oboljenja srca. Zamena G kodona A kodonom (75 G→A) u promotoru za Apo-A1 povezana je sa povišenim koncentracijama HDL holesterola, mada se oko ove tvrdnje još uvek vodi polemika, kao i oko nutrijenata koji bi ovakvu alteraciju mogli da izazovu. Neke studije pokazuju da je moguć uzrok ovakve alteracije unos polinezasićenih masnih kiselina, koje ne remete metabolizam samo ovog gena, već i gena koji kodiraju nekoliko enzima koji učestvuju u lipidnom metabolizmu i metabolizmu ugljenih hidrata. Evidentno je da su ovakve alteracije potpomognute unosom alkohola i pušenjem [35].

**Budućnost i etika**

Nutrigenomika se trenutno bavi definisanjem povezanosti između nutrijenata i odgovarajućih režima ishrane sa bolestima čija je genetska osnova poznata, a razvojem ove nauke i novim istraživanjima doći će do napretka medicine. Razvojem nutrigenomike započeto je sa komercijalizacijom suplemenata u ishrani. Neke laboratorije širom Amerike započele su sa marketinškom kampanjom genotipizacije i naknadnim savetovanjem za ishranu. Ovakve usluge dostupne su osobama širom sveta. S obzirom da su usluge ovakve vrste nove, naučnici postavljaju etička, legalna i socijalna pitanja (*ethical, legal and social issues – ELSI topics*) s obzirom da je sama genotipizacija velikom delu stanovništva nedostupna usled visoke cene. Još jedno etičko pitanje jeste bezbednost genoma individue nakon poveravanja informacija privatnim labratorijama, kao i ko će sve biti u kontaktu sa tim informacijama. Kanada je jedna od zemalja čiji su stanovnici započeli sa korišćenjem usluga koje nude laboratorije i istraživanja pokazuju da veliki udeo stanovništva veruje u to da su koristi nutrigenomike veće od eventualne štete, dok lekari iste zemlje iskazuju sumnju. Pored sumnje u korist, lekari sumnjaju u mogućnost tako brze integracije Internet usluga u sistem zdravstva. Naravno, koristi nutrigenomike su ogromne, međutim, postavlja se pitanje da li je nauka toliko odmakla da se sa kliničkih ispitivanja može preći odmah na usluge preko Interneta bez ličnog kontakta sa bolesnikom. Obe strane se slažu da je potrebno veće upoznavanje stanovništva sa realnim mogućnostima nutrigenomike i o tome dokle se za sada stiglo sa istraživanjima. Nutrigenomika je oblast u kojoj se nauka susreće sa industrijom i naučnici se utrkuju u patentiranju svojih pronalazaka. Takva žurba i uticaj industrije i njenih pravila zapostavlja bolesnike [11, 36–38].

Budućnost nutrigenomike leži u pronalaženju novih metoda ispitivanja za bioaktivne nutrijente, pronalaženje načina za sprovođenje ispitivanja populacije koje će biti dostupno svima. Takođe, važno je da se shvati kako metabolizam nutrijenata utiče na genski polimorfizam, kao i da se pronađu novi biomarkeri koji će u *in vivo* uslovima potvrditi delovanje nutrijenata [39, 40].

Animalni modeli ukazuju na mogućnost da se modifikacijom ishrane majke pre i u toku trudnoće može programirati šema ekspresije gena u embrionu koja će se održati sa godinama i sprečiti ili ublažiti nastanak bolesti [2]. Takve tvrdnje potiču iz 1996. godine kada su Joseph i Kramer [41] primetili fenomen malnutricije i metaboličkog imprintinga na animalnom modelu koji uslovljava poremećaj gena u potomstvu majki koje su se nepravilno hranjene u toku trudnoće. Pretpostavlja se da se taj primer može primeniti i na ljudsku populaciju jer ishrana majke utiče na genetski profil deteta [41]. Ovakav način „genske terapije" bio bi izuzetno uspešan, jer bi se primenio na čitav organizam bez komplikacija koje nosi injektovanje vektora genske terapije u krvotok odraslog čoveka.

Takođe, veruje se da će se pravilnom ishranom majki povećati lučenje korisnih elemenata u mleku koji su od izuzetnog značaja u ishrani, pravilnom razvoju i zdravlju odojčeta [42]. Neki od tih elemenata mogu imati protektivno i antioksidativno dejstvo i umanjiti ili eliminisati toksične efekte koje mogu proizvesti rezidue kontaminenata prisutnih u majčinom mleku [43, 44].

Genomske tehnologije omogućiće, takođe, da se odredi tačna količina potrebnog unosa pojedinih nutrijenata, kao i njihova toksična doza [2]. Veruje se da će se pravilnom ishranom sprečiti pojava gojaznosti, što bi u kombinaciji sa promovisanjem i prihvatanjem zdravog načina života dovelo do smanjenja incidencije brojnih oboljenja [13, 45].

**Zaključak**

Medicina prošlog veka u prvi plan je stavila farmaceutske proizvode i samim tim su lekari pripremani da bolesniku mogu da pomognu pre svega medikamentnom terapijom.

Nutrigenomika sa sobom donosi revolucionarne promene u ishrani, kako u kliničkoj praksi, tako i u svakodnevnom životu, jer omogućava ishranu baziranu na genetskoj strukturi svake individue, posebno u cilju prevencije, bolničku ishranu modifikovanu za svakog bolesnika na osnovu genetskog statusa i dijagnoze, kao i bolje prilagođenu ishranu šire populacije sa dodatkom mikronutrijenata koji povećavaju korist, a smanjuju neželjene efekte hrane.

Nutrigenomika koja nudi usavršavanje Hipokratove teorije da se bolesti najuspešnije leče adekvatnom ishranom, predstavlja šansu za pametniju, efikasniju i uspešniju prevenciju i lečenje oboljenja.

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Primljen 16. IX 2010.
Revidiran 08. X 2010.
Prihvaćen 08. X 2010.

CASE REPORT

UDC: 615.817:616.1-056.7
DOI:10.2298/VSP1109792J

# Successful implantation of a permanent pacemaker through a persistent left superior vena cava by using a right subclavian approach

## Uspešna implantacija trajnog vodiča ritma kroz perzistentnu levu gornju šuplju venu koristeći desni supklavikularni pristup

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**Abstract**

**Introduction.** Persistent left superior vena cava, a rare congenital abnormality, can complicate placement of pacemaker leads through the subclavian vein. A left-sided approach is usually preferable in such cases. **Case report.** We reported a case in which we began a single-chamber pacemaker implantation procedure *via* a right subclavian approach (because of scarring beneath the left clavicle) and then discovered intraoperatively that the patient had a persistent left superior vena cava. After a few attempts, we succeeded in placing the head of the electrode in the septum, near the top of the right ventricle, and the rest of the procedure was completed without complication. **Conclusion.** To our knowledge, this is the first reported case of pacemaker implantation, with passive electrode, through a persistent left superior vena cava *via* the right subclavian vein. This case demonstrates that such an approach, when necessary, can be used successfully.

**Key words:**
**vena cava, superior; congenital abnormalities; subclavian vein; pacemaker, artificial; heart catheterization.**

**Apstrakt**

**Uvod.** Leva gornja šuplja vena, retka kongenitalna anomalija, može komplikovati pozicioniranje elektrode trajnog vodiča ritma kroz venu supklaviju. U ovakvim slučajevima, obično se koristi levostrani supklavikularni pristup. Mi prikazujemo slučaj u kome smo započeli proceduru implantacije jednokomorskog vodiča ritma kroz desnu venu supklaviju (zbog velikog ožiljka u predelu ispod leve supklavije) i u toku procedure otkrili smo da bolesnik ima perzistentnu levu šuplju venu. Nakon nekoliko pokušaja, uspeli smo sa pozicioniranjem elektrode u septum, blizu vrha desne komore i ostatak procedure je završen bez komplikacija. **Zaključak.** Prema našem znanju, ovo je prvi prijavljeni slučaj implantacije trajnog vodiča ritma, pasivnom elektrodom, kroz perzistentnu levu gornju šuplju venu koristeći desni supklavikularni pristup. Opisani slučaj pokazuje da ovakav pristup, kada je neophodno, može uspešno da se koristi.

**Ključne reči:**
**v. cava superior; anomalije; v. subclavia; elektrostimulator srca; kateterizacija srca.**

### Introduction

Persistent left superior vena cava is a relatively rare persistent congenital anomaly [1–3]. Its estimated prevalence is about 0.3% in the general population and up to 4.4% in patients with congenital heart disease [4]. This condition, often found incidentally, can complicate the placement of pacemaker leads through subclavian routes [5–7]. We reported a case of successful single-chamber pacemaker implantation through a persistent left superior vena cava by using a right subclavian approach.

### Case report

An 88-year-old man with a long history of hypertension, diabetes mellitus, and adenoma of the prostate was admitted to our hospital for implantation of a permanent pacemaker. A holter electrocardiogram (ECG) showed atrial fibrillation with 482 pauses of more than 2 seconds and 14 pauses of more than 2.5 seconds. All episodes were registered during the night.

Echocardiography revealed a preserved ejection fraction of 55% and a left ventricle of normal dimensions. The

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left atrial diameter was 4.5 cm. There was a mild aortic regurgitation and mild to moderate mitral regurgitation. A chest radiogram was normal. An ECG showed atrial fibrillation with heart rate of about 60 beats per minute.

After medical preparation with 10 mg intramuscular diazepam, the patient was sent to the catheterization laboratory to receive a permanent pacemaker. We used the right subclavian approach to introduce a wire, because the patient had a large scar on the left side of the chest under the clavicle. We made 3 attempts to advance the wire into the superior vena cava, but we were unsuccessful because the wire was going in the wrong direction, toward the left side of the heart and downward.

We then performed contrast-enhanced computed tomography of the right heart system (Figure 1) and noticed the persistent left superior vena cava. We continued the procedure, knowing that the right subclavian approach we had used would make it difficult to introduce the electrode into the right ventricle through the left superior vena cava. After few attempts, we succeeded in placing the head of the electrode in the septum, near the top of the right ventricle (Figure 2).


**Fig. 1 (a and b) – Contrast-enhanced computed tomographic angiograms of the right heart vessel system**

**Fig. 2 – A chest radiograph showing VVI pacing through the patient's left superior vena cava**

There were no other complications of the procedure, and the patient was stable throughout it. We achieved a stimulation threshold with an amplitude of 0.5 V and a pulse width of 0.48 ms. Electrode resistance was 840 ohms.

Six months after the pacemaker implantation, the patient was doing well, and the pacemaker's electronic controls showed normal functioning.

## Discussion

The left superior vena cava complicates pacemaker implantation. All implantations of pacemakers through the left superior vena cava that have been described in the literature to date have been done from the left side, through the left subclavian vein[5–9]. The right subclavian approach, when necessary, is even more complicated than the left-sided approach. An additional problem is that the long distance that has to be traversed to reach the apex of the right ventricle exceeds the standard length of the pacemaker's lead. In our case, at the end of the procedure, only a short segment of the electrode extended out of the body, just enough to connect to the generator.

Our case differs from previously reported cases of pacemaker implantation through a persistent left superior vena cava, because we did it from the right side, through the right subclavian vein. Undeniably, in these situations, a left-sided approach is preferable. However, in situations when a left-sided approach is not possible, it is good to know that, although it is more difficult, a right-sided approach is an option.

## Conclusion

To our knowledge, this is the first reported case of pacemaker implantation, with passive electrode, through a persistent left superior vena cava *via* the right subclavian vein. This case demonstrates that such an approach, when necessary, can be used successfully.

## Acknowledgment

Stephen N. Palmer, PhD, ELS, contributed to the editing of this manuscript.

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Received on January 25, 2010.
Revised on March 15, 2010.
Accepted on April 11, 2010.

P R I K A Z S L U Č A J A

UDC: 616.42-03/-08::617.541/.542
DOI:10.2298/VSP1109795M

# Hirurško lečenje lokalizovanog oblika Kastlemanove bolesti plazmaćelijskog histološkog tipa

## Surgical treatment of unicentric plasma cell histological type Castleman's disease

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**Apstrakt**

**Uvod.** Kastlemanova bolest ili angiofolikularna limfoidna hiperplazija je retko oboljenje sa dve identifikovane kliničke forme: unicentrični ili lokalizovani oblik koji se odlikuje izolovanim uvećanjem limfnih čvorova, najčešće u medijastinumu, i multicentrični oblik koji se ispoljava kao sistemska bolest sa raširenom limfadenopatijom, organomegalijom i prisustvom opštih simptoma bolesti. Histološki se razlikuju hijalinovaskularni, plazmaćelijski i prelazni (mešani) ćelijski tip. **Prikaz bolesnika.** U radu je prikazana bolesnica, stara 59 godina, sa unicentričnim oblikom Kastlemanove bolesti plazmaćelijskog tipa. Unicentrični oblik obično se ispoljava histološki kao hijalinovaskularni tip, izuzetno retko kao plazmaćelijski tip, dok prelazni (mešani) ćelijski tip nije do sada opisan u literaturi kod lokalizovane kliničke forme. Oboljenje se manifestovalo bolovima u grudnom košu, gubitkom telesne mase, zamaranjem i slabošću donjih ekstremiteta. Ispitivanjem je utvrđeno postojanje uvećanih limfnih žlezda, desno paratrahealno u bliskom kontaktu sa gornjom šupljom venom. Bolest je potvrđena histopatološkom analizom biopsije medijastinalne limfne žlezde nakon medijatinoskopije. Primenjeno je hirurško lečenje (desna torakotomija) i ekstirpacija uvećanih limfnih žlezda. Nakon urednog postoperativnog toka, konstatovan je potpuni terapijski odgovor. **Zaključak.** Unicentrični oblik Kastlemanove bolesti ispoljava se uvećanjem limfnih čvorova na predilekcionim mestima, najčešće u medijastinumu. Hirurško lečenje je metoda izbora koja dovodi do potpunog oporavka.

**Ključne reči:**
**kastlemanova bolest; hirurgija, torakalna, procedure; dijagnoza; lečenje, ishod.**

**Abstract**

**Introduction.** Castleman's disease or angiofollicular lymph hyperplasia is a rare disease with two identified clinical forms. Unicentric or localized form is characterized by isolated growth of lymph nodes, most often in mediastinum, and multicentric form is expressed as systemic disease with spread lymphadenopathy, organomegaly and presence of general symptoms of the disease. Histological types are hyalovascular, plasma-cell and transitive (mixed) cell. **Case report.** This case report shows a woman, 59 years old, with unicentric form of plasma-cell type of Castleman's disease. Unicentric form is usually shown as hyalovascular histological type, extremely rare as plasma-cell type, and transitive (mixed) cell type was never described in literature as localized clinical form. The disease was manifested with chest pain, loss of body weight, exhaustion and weakness of legs. Further diagnostic procedures found the presence of enlarged lymph nodes paratracheally right, in a close contact with vena cava superior. The disease was confirmed by histopathological analysis of bioptated mediastinal lymph node after mediastinoscopy. Surgical treatment included extirpation of enlarged lymph nodes. After the regular postoperative condition, a full therapy effect was confirmed. **Conclusion**. Unicentric form of Castleman's disease is expressed with enlarged lymph nodes on predilected places, usually in mediastinum. Surgical treatment is best method for the management of the disease and brings a full recovery of patient.

**Key words:**
**castleman disease; thoracic surgical procedures; diagnosis; treatment outcome.**

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## Uvod

Kastlemanova bolest je retko, atipično limfoproliferativno oboljenje [1, 2]. Precizna incidencija nije do danas poznata. Lokalizovana forma je najčešća i opisana je prvi put od strane Kastlemana 1956. godine [3]. Etiologija bolesti je nepoznata. Ključna uloga se pripisuje povećanoj produkciji interleukina-6 (IL-6), a prema nekim autorima i infekciji humanim herpes virusom 8 (HHV 8) [4–8].

Kliničke manifestacije bolesti variraju od asimptomatskog uvećanja jedne grupe žlezda, najčešće u medijastinumu, do sistemske bolesti sa raširenom limfadenopatijom, organomegalijom i prisustvom opštih simptoma bolesti. Kada pridruženo postoji polineuropatija, organomegalija, edemi ili izlivi, endokrinopatija, M-protein i promene na koži, tada se taj oblik multisistemske bolesti naziva sindrom POEMS [1–9]. Smatra se da je multicentrični oblik bolesti češći. Na Prvoj internacionalnoj konferenciji o Kastlemanovoj bolesti održanoj u Santa Feu 2005. godine procentualni odnos bio je 70,21% multicentrične bolesti naspram 29,79% lokalizovane forme (hijalinovaskularni tip 27,67%, plazmaćelijski 2,13% i mešani 0 %).

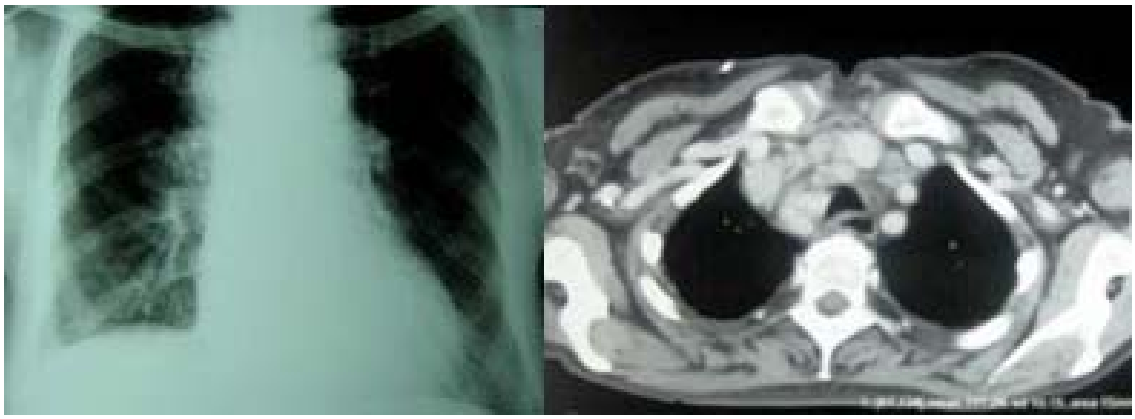
Klinički oblik bolesti određuje terapijski pristup. Kod sistemske bolesti optimalni oblik lečenja nije utvrđen. Kombinacija različitih terapijskih protokola uključujući hirurgiju i različite oblike imunosupresivne terapije nije dovela do povoljne prognoze bolesti [10, 11].

Lokalizovani oblik bolesti obično je benignog toka i hirurško lečenje je optimalan terapijski postupak. Najčešći histološki tip lokalizovane bolesti je hijalinovaskularni koji je asimptomatski ili postoje tegobe koje izaziva tumorska kompresija. Izuzetno retko manifestuje se kao plazmaćelijski histološki tip koji je lokalizovan, ali pored simptoma uzrokovanih tumorskom kompresijom postoje i sistemski znaci bolesti. Prelazni ćelijski histološki tip nije do sada zabeležen kao lokalizovani oblik bolesti.

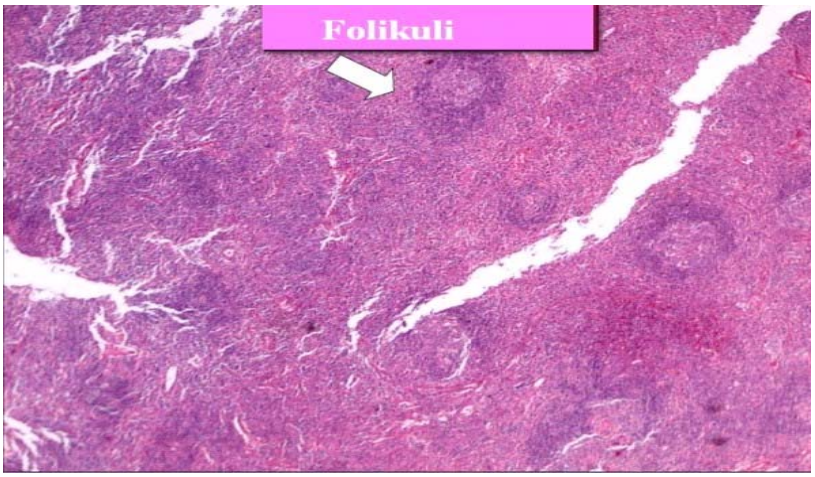
U radu je prikazana bolesnica sa unicentričnim oblikom Kastlemanove bolesti plazmaćelijskog histološkog tipa. Analizirana je klinička slika, dijagnostički i terapijski postupci.

## Prikaz bolesnika

Bolesnica, stara 59 godina, hospitalizovana je zbog proširene medijastinalne senke viđene običnom radiografijom i kompjuterizovanom tomografijom (KT) grudnog koša (slike 1 i 2). Radiografska dijagnostika sprovedena je zbog pojave bolova u grudnom košu, zamaranja i nedostatka vazduha pri fizičkom naporu, malaksalosti, gubitka telesne mase i povremene supfebrilnosti. U razgovoru sa bolesnicom utvrđeno je da je dugogodišnji pušač, da su izraženije tegobe počele



**Sl. 1 – Radiografski nalaz i kompjuterizovana tomografija (KT) grudnog koša (konglomerat limfnh žlezda, paratrahealno desno, približnih dimenzija 50 × 47 mm)**




**Sl. 2 – *Plasmacytosis reactiva*, kappa/lambda, poliklonski fenotip atrofičnih lakih lanaca u interfolikularnim prostorima sa koncentričnom sitnoćelijskom *mantle cell* zonom i PAS+ depozitima centralno; između plazma ćelija je proliferisana vaskularna mreža**

dva meseca pre prijema u kliniku, a prvi simptomi, u vidu malaksalosti, šest meseci ranije. Bolesnica do pojave ovih tegoba nije bolovala od težih bolesti, niti je ranije bila operisana. Jedino je navela da se leči od arterijske hipertenzije u poslednje dve godine, bez upotrebe drugih lekova osim antihipertenziva.

Proširena medijastinalna senka bez vidljivih patoloških promena u plućima diferencijalnodijagnostički je upućivala na limfadenopatiju različite geneze ili tumor medijastinuma.

Prilikom prijema bolesnica je bila supfebrilna (37,6ºC) i otežano je hodala. Kliničkim pregledom nije uočeno postojanje periferne limfadenopatije. U laboratorijskim analizama krvi nađeno je: SE 20 mm/h, leukociti $14,2 \times 10^9$/L (neutrofili 57,3%, limfociti 23,9%, monociti 7,61%, eozinofili 8,53%, bazofili 2,66%), eritrociti $5,59 \times 10^{12}$/L, hemoglobin 149 g/L, hematokrit 46,1, trombociti $648 \times 10^9$/L, albumini 37 g/L.

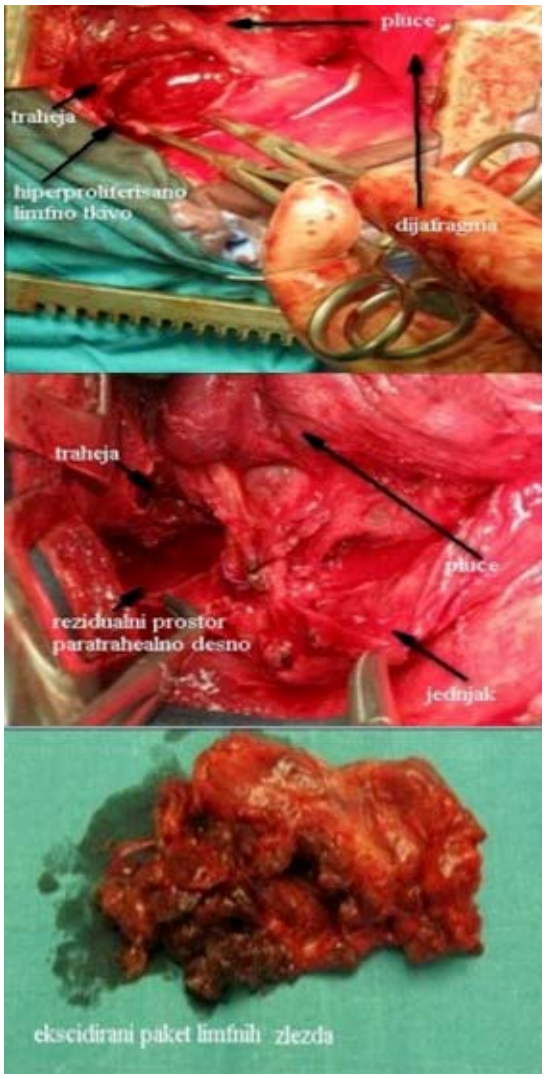
Bronhoskopski bio je opisan uredan nalaz u larinksu, traheji i levom bronhijalnom stablu, a desno je nađena proširena karina traheje, kao i gornja interlobarna karina uz znake ekstramuralne kompresije na bronh za gornji režanj. Urađena je transkarinalna aspiraciona iglena biopsija kroz račvu dušnika i gornju interlobarnu karinu, kao i biopsija sluzokože gornje interlobarne karine. Citološki nalaz iz transkarinalne aspiracione iglene biopsije bio je suspektan na hronično limfoproliferativno oboljenje, ali iz poslatog materijala nije bila moguća histološka potvrda bolesti.

Cervikalnom medijastinoskopijom pristupljeno je solidnoj masi koja je makroskopski imponovala kao konglomerat limfnih žlezda međusobno čvrsto adheriranih i hipervaskularizovanih. Bioptiran je čvorast isečak tkiva prečnika oko 5 mm, sivoružičaste boje koji je u celini uzet u jedan kalup. Urađena je imunohistohemijska analiza: CD20, kappa, lambda i histohemijska analiza Re i PAS. Zaključak patologa bio je da se radi o netumorskoj promeni tipa Kastlemanove bolesti plazmocitoidnog podtipa (slika 2).

Nakon postavljanja dijagnoze rađena je dodatna dijagnostička obrada u cilju utvrđivanja kliničke forme bolesti s obzirom na to da se plazmaćelijski histološki tip Kastlemanove bolesti javlja retko (oko 2%) i ispoljava kao lokalizovana klinička forma. Urađeni su KT pregledi abdomena i male karlice sa posebnim osvrtom na potencijalno uvećane limfne čvorove u retroperitoneumu. Nalaz je bio uredan. Rezultati virusološke analize seruma bili su sledeći: humani virus imunodeficijencije (anti HIV) negativan i herpes simpleks virus 1 (anti HSV1) pozitivan. Ponovljen bronhoskopski nalaz sa biopsijom bronha bio je uredan.

Nakon završetka dijagnostičkih postupaka bolest je označena kao klinički lokalizovani oblik Kastlemanove bolesti (*hyperplasio angiofollicularis lymphonodi*) i to plazmaćelijskog histološkog tipa.

Odlučeno je da se pristupi hirurškom lečenju i odstranjivanju mase iz medijastinuma pristupom kroz desnu torakotomiju. Intraoperativno nisu viđene patološke promene u plućnom parenhimu. Uočena je masa koja je makroskopski imponovala kao konglomerat uvećanih limfnih žlezda približnih dimenzija $5 \times 4 \times 5$ cm anatomski lociran između dušnika i gornje šuplje vene sa propagacijom distalno ka supkarinalnoj regiji i jednjaku, u adherentnom kontaktu sa pomenutim strukturama, bez njihove infiltracije. Promena je bila u celosti ekstirpirana (slika 3).




**Sl. 3 - Intraoperativni nalaz sa prikazom hiperproliferativnog limfnog tkiva, rezidualnim prostorom paratrehealno desno i ekscidiranim paketom limfnih žlezda**

Hirurška intervencija bila je praćena intenzivnim krvarenjem. Paketi limfnih žlezda bili su hipervaskularizovani. Kastlemanova bolest, inače, karakteriše se hiperplazijom folikula i vaskularnih elemenata limfnih žlezda što povećava rizik od perioperativnog krvarenja. Rizik se prevenira adekvatnom hirurškom tehnikom i, u poslednje vreme, preoperativnom embolizacijom arterijskih sudova pet do sedam dana pre planiranog hirurškog lečenja [12–14]. Postoperativni tok je protekao uredno.

Definitivnim patohistološkim nalazom potvrđena je dijagnoza dobijena nakon medijastinoskopije. Bolesnica je otpuštena iz bolnice 12. postoperativnog dana u dobrom opštem stanju.

Na kontrolnom pregledu nakon tri meseca konstatovan je potpuni terapijski efekat primenjenog hirurškog lečenja. Bolesnica je negirala tegobe u vidu malaksalosti i ubrzanog

zamaranja, sve vreme bila je afebrilna i samostalno pokretna. Laboratorijske analize bile su u granicama referentnih vrednosti. Vrednosti nespecifičnih faktora upale bili su: SE 10 mm/h, C-reaktivni protein 2,81 mg/L. Kontrolnim KT pregledom grudnog koša nije uočena medijastinalna limfadenopatija. Zaključeno je da je primenjenim hirurškim lečenjem postignut potpun terapijski odgovor i da ne postoji potreba za dodatnim lečenjem.

**Diskusija**

Kastlemanova bolest je prvi put opisana kao džinovska hiperplazija limfnih čvorova u medijastinumu [3]. Od tada do danas ovo oboljenje označavano je sa puno sinonima od kojih su najpoznatiji: folikularni limforetikulom, angiofolikularna hiperplazija limfnih žlezda, džinovska hiperplazija limfnih žlezda, benigni džinovski limfom i limfoidni hamartom.

Kastlemanova bolest odlikuje se heterogenom simptomatologijom i niskom incidencijom što otežava njeno dijagnostikovanje i lečenje. Oboljenje se češće javlja kod mlađih osoba [15]. Klinički se manifestuje unicentričnom (lokalizovanom) ili multicentričnom prezentacijom. Patohistološka klasifikacija razlikuje hijalinovaskulani tip koji je najčešći kod unicentričnog oblika bolesti, kao i plazmaćelijski i mešani tip koji se češće nalaze kod multicentričnog tipa bolesti [16].

U novije vreme interesovanje za ovu bolest poraslo je jer je vrlo često udružena sa HIV infekcijom [17]. Etiologija i patogeneza bolesti je nedovoljno poznata. Humani herpes virus tip 8 (HHV-8) je prisutan kod skoro svih bolesnika obolelih od Kastlemanove bolesti udružene sa HIV infekcijom, ali i kod nekih koji nisu inficirani HIV-om. U mnogim studijama analizirana je sprega između kvantiteta HHV-8 DNA kod obolelih od Kastlemanove bolesti i intenziteta simptoma ovog oboljenja. Smatra se da postoji izvesna etiološka uloga HHV-8 u pojedinim slučajevima Kastlemanove bolesti, ali da je mnogo češće virus obični „posmatrač“ posebno kod bolesnika inficiranih HIV-om [16].

Inflamacijski medijatori imaju važnu ulogu u etiopatogenezi ovog oboljenja. Humani IL-6 je snažni stimulus proliferacije B-ćelija. Primećeno je da kod ovog oboljenja postoji povećana produkcija IL-6, a on indukuje produkciju humanog vaskularnog endotelnog faktora rasta i angiogeneze, te dodatno stimuliše proliferaciju B-ćelija. Ostali mogući inflamacijski medijatori u razvoju Kastlemanove bolesti su epidermalni faktor rasta i interferon alfa [18].

Klinički, oboljenje se manifestuje kao lokalizovani (unicentrični) ili generalizovani (multicentrični) oblik. Unicentrični sa hijalinovaskularnim histopatološkim ćelijskim tipom je najčešći oblik ispoljavanja lokalizovane bolesti (> 90%). Javlja se u svim starosnim grupama, ali najčešće u trećoj deceniji života. Manifestuje se uvećanjem jedne ili grupe limfnih žlezda. Plazmaćelijski histološki tip javlja se predominantno u šestoj deceniji života.

Lokalizovana bolest obično je asimptomatska, mada kliničke karakteristike variraju od slučaja do slučaja i mogu se manifestovati bolom zbog lokalnog širenja tkiva. Najčešće lokalizacije su medijastinum, trbuh i aksilarna regija, mada se bolest može praktično pojaviti u bilo kojoj regiji organizma [19, 20]. Sistemski simptomi i laboratorijske abnormalnosti kod unicentričnog oblika su retkost.

Multicentrični oblik odlikuje se generalizovanom limfadenopatijom; češće su zahvaćene periferne limfne žlezde nego medijastinalne. Obično je udružen sa sistemskim manifestacijama kao što su noćno znojenje, povišena temperatura i gubitak telesne mase. Kada se istovremeno pojave polineuropatija, organomegalija, endokrinopatija, edemi ili izlivi, M-protein i promene na koži, oboljenje se označava kao multisistemsko i naziva se sindrom POEMS ili sindrom Crow-Fukase. Kod njega je najčešće prisutan HHV-8 virus [9, 10].

Kod naše bolesnice utvrđeno je postojanje unicentričnog oblika Kastlemanove bolesti plazmaćelijskog histološkog tipa. U laboratorijskim analizama postojale su povišene vrednosti nespecifičnih fakora zapaljenja. Bolesnica je bila HSV-1 pozitivna. Zbog postojanja opštih simptoma bolesti: malaksalosti, povišene temperature, noćnog znojenja i gubitka telesne mase, a radiografski uočene proširene senke u medijastinumu, postavljena je sumnja na postojanje limfoproliferativnog oboljenja. Definitivna dijagnoza je postavljena biopsijom limfne žlezde nakon medijastinoskopije. Patohistološke odlike obolelog tkiva bile su prisustvo velikih folikula odvojenih proliferisanim vaskularnim limfnim tkivom koje sadrži limfocite i obilje plazma ćelija.

U zavisnosti od histopatološkog nalaza oboljenje se klasifikuje kao hijalinovaskularni, plazmaćelijski i prelazni (mešani) ćelijski tip bolesti. Hijalinovaskularni tip ispoljava se kod oko 90% slučajeva kao lokalizovana bolest, dok se plazmaćelijski i mešani ćelijski tip obično nalaze kod multicentrične bolesti.

Kod prikazane bolesnice utvrđen je lokalizovani oblik bolesti plazmaćelijskog histološkog tipa. Retka pojava i heterogenost simptoma, kao i studije rađene na malim serijama bolesnika nisu definisale precizan terapijski postupak kod ove bolesti. Unicentrični oblik uglavnom se leči ekscizionom hirurgijom, recidivi su retki i prognoza je povoljna. U pojedinim slučajevima kada operacija nije izvodljiva primenjuje se zračna terapija ili, ukoliko je bolest asimptomatska, samo opservacija.

Multicentrični oblik je vrlo retko asimptomatski te se ekscizionom hirurgijom postiže samo prolazni „*debulking*“ efekat olakšanja tegoba. Bolesnici sa ovim tipom bolesti skoro uvek zahtevaju sistemsku terapiju. Obično lečenje počinje kortikosteroidima, kod težih oblika primenjuje se kombinovana hemioterapija a opisano je i lečenje talidomidom i antivirusnim lekom rituksimabom [21–23].

Prikazana bolesnica je zanimljiva zato što je imala kliničku sliku sa ispoljenim sistemskim znacima bolesti i nakon medijastinoskopije dokazan plazmaćelijski histološki tip što je, takođe, upućivalo na multicentrično ispoljavanje bolesti. S obzirom da radiografska dijagnostika nije pokazivala druge lokalizacije uvećanih limfnih žlezda urađeno je dodatno kliničko i radiološko snimanje celog tela, nakon čega je zaključeno da se radi o lokalizovanom obliku bolesti i da treba pristupiti hirurškom lečenju i potpunom odstranjivanju hiperproliferisanog žlezdanog tkiva. Na kontrolnom pregledu nakon tri meseca konstatovan je potpuni pozitivan efekat primenjenog lečenja. Bolesnica je bila bez tegoba, laboratorijske analize su bile u granicama referentnih vrednosti, uz povećanje telesne mase od pet kilograma.

**Zaključak**

Kastlemanova bolest je retko atipično limfoproliferativno oboljenje. Dijagnoza bolesti se postavlja patohistološkom analizom nakon biopsije. Unicentrični oblik bolesti ispoljava se uvećanjem limfnih žlezda na predilekcionim mestima, najčešće u medijastinumu. Oboljenje je obično asimptomatsko i hijalinovaskularnog ćelijskog tipa, dok se retko manifestuje sistemskim znacima bolesti i kao plazmaćelijski histološki tip.

Hirurško lečenje lokalizovanog oblika bolesti je metoda izbora koja dovodi do potpunog oporavka.

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Primljen 5. I 2010.
Revidiran 25. VI 2010.
Prihvaćen 1. VII 2010.

P R I K A Z S L U Č A J A

UDC: 617.7-089
DOI:10.2298/VSP1109800N

# Istovremena fakoemulzifikacija, implantacija sočiva i endotelna keratoplastika (trostruka procedura)

## Simultaneous phacoemulsification, lens implantation and endothelial keratoplasty (triple procedure)

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**Apstrakt**

**Uvod.** Istovremeno izvođenje endotelne keratoplastike, fakoemulzifikacije i implantacije intraokularnog sočiva indikovano je kod Fuksove distrofije udružene sa kataraktom. Prednosti nad standardnom kombinacijom koja uključuje perforativnu keratoplastiku su: bešavna hirurgija kroz mali otvor na limbusu, brži oporavak, manje problema sa površinom rožnjače, manji astigmatizam, veća čvrstina rožnjače i tačnije sračunavanje dioptrijske vrednosti intraokularnog sočiva. Cilj studije bio je da, po prvi put u našoj literaturi, opišemo primenu ove tehnike istovremene operacije. **Prikaz bolesnice**. Bolesnica, stara 76 godina, imala je tegobe zbog postepenog smanjivanja oštrine vida oba oka. Korigovana oštrina vida desnog oka bila je 0,3, a levog 1/60, pahimetrijske vrednosti 590 μm, odnosno 603 μm. Bila je prisutna izražena *cornea guttata.* U oba oka postojala je nuklearna katarakta. Na levom oku prvo je urađena fakoemulzifikacija i implantacija intraokularnog sočiva, a onda i svlačenje Descemetove membrane zajedno sa endotelom rožnjače. Kroz otvor na limbusu, proširenim na 5 mm, unesen je lamelarni transplantat rožnjače, prečnika 8,0 mm i debljine oko 150 μm, savijen napola, sa endotelnom stranom unutra. U prednjoj očnoj komori, kalem je razvijen i vazduhom priljubljen za ogoljenu stromu primaoca. Tokom dve godine, kalem je ostao priljubljen i providan. Oštrina vida posle dva meseca bila je 0,5, a posle godinu dana 0,8. **Zaključak.** Nova tehnika istovremene endotelne keratoplastike, fakoemulzifikacije i implantacije sočiva pokazala se kao dobar izbor za lečenje početne Fuksove distrofije rožnjače udružene sa kataraktom.

**Ključne reči:**
**fakoemulzifikacija; tranplatacija endotela rožnjače sa descemetovom membranom; sočivo, intraokularna implantacija.**

**Abstract**

**Introduction.** Simultaneous Descemet stripping endothelial keratoplasty, phacoemulsification, and intraocular lens implantation are indicated in Fuchs' dystrophy with associated cataract. Compared to the standard method of the triple procedure which includes penetrating keratoplasty, this new method has the advantages of sutureless surgery, small limbal incision, faster recovery, less surface problems, less astigmatism, stronger tensile strength and more predictable calculation of the intraocular lens power. This is the first report of such a combination of procedures in our literature. **Case report.** A 76-year-old woman suffered from a gradual bilateral visual loss. The best corrected visual acuity was 20/60 (right eye) and finger counting at 1m (left eye). Corneal thickness was 590 μm and 603 μm, respectively. A marked cornea guttata and nuclear cataract were present in both eyes. Phacoemulsification, lens implantation, and Descemet stripping were done in the left eye. The posterior lamellar corneal graft, 8.0 mm in diameter and about 150 μm thick, was bent and inserted through the limbal incision. The air was injected into the anterior chamber to attach the graft to the recipient stroma. The cornea remained clear, and the transplant was attached during a two-year follow-up. Visual acuity was 20/40 after two months, and 20/25 after one year. **Conclusion.** The new technique proved itself as a good choice for the treatment of a mild Fuchs' dystrophy associated with cataract.

**Key words:**
**phacoemulsification; descemet stripping endothelial keratoplasty; lens implantation, intraocular.**

### Uvod

Trostruka procedura označava istovremeno uklanjanje katarakte, ugrađivanje intraokularnog sočiva i presađivanje rožnjače.

Pre gotovo 35 godina, u našoj zemlji su prvi put, u istom aktu, izvedene perforativna keratoplastika i intrakapsularna krioekstrakcija katarakte [1]. U to vreme, ova procedura bila je prilična retkost zbog opasnosti od horoidalnog krvavljenja i gubitka sadržaja očne jabučice tokom operacije na

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oku sa velikim otvorom. Isto tako, prolaps staklastog tela prilikom ekstrakcije sočiva pretio je da ugrozi sudbinu kalema rožnjače jer su mogućnosti za izvođenje dobre prednje vitrektomije bile ograničene [2].

Nešto kasnije, keratoplastika je rađena simultano sa ekstrakapsularnom ekstrakcijom katarakte, a onda je i tvrdo veštačko sočivo hapticima smeštano u cilijarni sulkus. Opasnost od ekspulzivne hemoragije ostala je zbog operacije na oku sa velikim centralnim otvorom, ali je snižena učestalost prolapsa staklastog tela i edema makule [3].

Zatim je došlo do velikog sažimanja operacije katarakte novim, ultrazvučnim metodom i stvaranja mekih, savitljivih intraokularnih sočiva koja su, tokom trostruke procedure zbog manjih centralnih leukoma, mogla da se ugrade kroz mali otvor na limbusu, umesto kroz veliki centralni otvor u rožnjači, pod „otvorenim nebom". Leukom bi onda bio uklonjen standardnom perforativnom keratoplastikom.

Najzad, na samom kraju 20. veka, a naročito od 2004. godine, neke bolesti rožnjače počinju uspešno da se leče selektivnom transplantacijom obolelih slojeva. Za hirurško lečenje hroničnog edema rožnjače izazvanog oštećenjem endotela nije više neophodna perforativna keratoplastika, kojom se presađuju svi slojevi rožnjače. Dovoljna je i moguća samo transplantacija endotela sa Descemetovom membranom, na tankom nosaču strome. Ova operacija je prvo nazvana endotelna keratoplastika (EK) [4]. Kalem se ne ušiva, već se potiskuje bulom vazduha ubrizganog u prednju očnu komoru. Njena usavršena varijanta nosi ime endotelna keratoplastika sa svlačenjem Descemeta (*Descemet stripping endothelial keratoplasty – DSEK*) [5, 6].

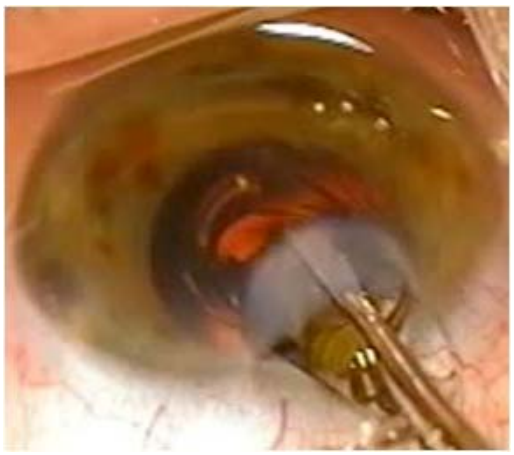
Pri postojanju početne Fuksove distrofije rožnjače udružene sa kataraktom, moguće je istovremeno izvođenje fakoemulzifikacije, implantacije savitljivog sočiva i DSEK. Time se sve hirurške radnje obavljaju bešavno, kroz mali otvor na limbusu [7]. Po prvi put u našoj literaturi, opisujemo jednu takvu operaciju posle praćenja tokom dve godine.

**Prikaz bolesnika**

Bolesnica, stara 76 godina, primljena je zbog postepenog slabljenja vida na oba oka tokom poslednje tri godine. Arterijsku hipertenziju dobro je regulisala lekovima. Oštrina vida desnog oka bila je 0,3, sa korekcijom od 2,25 dioptrije sfere, dok je vizus levog oka bio sveden na brojanje prstiju na 1 m. Intraokularni pritisak bio je 12 mmHg na desnom, a 16 mmHg na levom oku. Površina rožnjače bila je bez promena. Postojala je izražena *cornea guttata* sa lakim edemom strome. Katarakta je bila nuklearna. Fundus se nije video sasvim jasno, ali je izgledao bez promena. Debljina rožnjače bila je 590 μm na desnom oku i 603 μm na levom.

Operacija levog oka izvedena je u parabulbarnoj anesteziji bupivakainom. Glavna incizijia, dužine 2,8 mm, načinjena je u rožnjači na 12 h, a dve bočne incizije na 10 i 2 h. U komoru je ubrizgan prvo viskoelastik male gustine, pa onda viskoelastik velike gustine. Pod viskoelastik ubrizgana je boja tripan plavo. Prednja kapsula sočiva je zacepljena vrhom savijene insulinske igle. Tako stvoren jezičak uhvaćen je pincetom za kapsuloreksu i vučen ukrug dok se nije načinio kružni otvor prečnika oko 5,5 mm u prednjoj kapsuli. Zatim je ubrizgan fiziološki rastvor natrijum hlorida pod prednju kapsulu, a onda i u korteks kristalnog sočiva, čime su napravljene hidrodiseksija i hidrodelineacija. Sondom za fakoemulzifikaciju pravljen je rov od 12 h do 6 h u jedru sočiva, sve dok se nije pojavio crveni refleks (slika 1). Stavljanjem sonde i čopera uz ivice na dnu rova i njihovim razdvajanjem, jedro je polomljeno napola. Svaka od polovina vakuumom je fiksirana za sondu, a čoperom podeljena na još dva dela. Sva četiri komada nukleusa su fakemulzifikovana. Korteks je uklonjen sistemom za aspiraciju i irigaciju. Implantacija savitljivog sočiva u kapsulnu vrećicu izvršena je posle ubrizgavanja viskoelastika u taj prostor i proširenja otvora na limbusu do 3,2 mm (slika 2).

**Sl. 1 – Prva od tri procedure: fakoemulzifikacija**



**Sl. 2 – Druga procedura: implantacija sočiva**

Sav viskoelastik je onda pažljivo uklonjen iz oka, a na ulazni otvor stavljen jedan šav 10–0 monofilamenta od najlona. U komoru je opet ubrizgana boja tripan plavo, pa isprana fiziološkim rastvorom natrijum-hlorida. Trepanom prečnika 8,0 mm lagano je pritisnuta površina rožnjače da bi se obeležila veličina kalema. Descemet je raskidan obrnutom Sinskijevom kukom po kružnici koja je bila u projekciji belega na površini rožnjače. Descemetova membrana i endotel su odvajani Prajsovom kukom sa irigacijom, a onda uklanjani iz oka. Tako je u rožnjači primaoca nastala kružna površina ogoljene strome prečnika 8,0 mm.

Kalem je pripreman manuelnom disekcijom rožnjače davaoca pomoću spatule uvedene kroz vertikalnu inciziju na limbusu koja je načinjena nožem sa graničnikom podešenim na dubinu od 0,5 mm. Tako raslojena rožnjača trepanirana je sa endotelne strane, čime su dobijena dva kalema prečnika 8,0 mm. Onaj tanji, debljine oko 150 µm, sadržao je Descemetovu membranu i endotel i korišćen je za transplantaciju. Pošto mu je na endotelnu stranu stavljena kap viskoelastika, on je savijen napola, sa endotelom unutra i unesen u prednju očnu komoru kroz inciziju proširenu na 5,0 mm. Tu je razvijen i priljubljen za stromu rožnjače primaoca pomoću bule vazduha. Incizija je ponovo ušivena suturom 10–0 najlona.

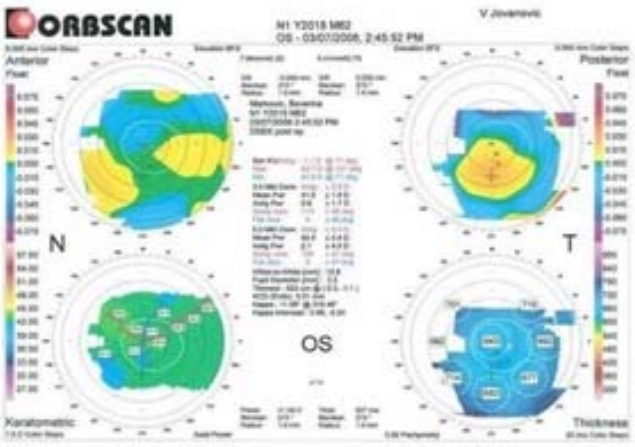
Na četiri mesta načinjena je incizija rožnjače, od površine do spoja kalema i rožnjače primaoca (*ineterface*, IF) (slika 3). Kroz njih je istiskivana zaostala tečnost sa IF prevlačenjem Lindstremovog rolera preko površine rožnjače. Na kraju operacije, supkonjunktivalno su ubrizgani kortikosteroid i gentamicin. Intravenski je dato 100 mL 20% manitola.

**Sl. 3 – Treća procedura: endotelna keratoplastika posle svlačenja Descemetove membrane (pravljenje incizije za drenažu tečnosti sa spoja kalema i rožnjače primaoca)**

U postoperativnom periodu, ukapavani su kortikosteroid, šest puta, i antibiotik iz grupe hinolona, četiri puta na dan tokom nedelju dana, a onda samo kortikosteroid četiri puta dnevno tokom tri meseca, dva puta dnevno još tri meseca, a onda jednom dnevno do kraja perioda praćenja.

Kalem je ostao providan i priljubljen za rožnjaču primaoca tokom celog perioda praćenja (slika 4). Već sedmog dana posle operacije, korigovana oštrina vida bila je 0,5. Dva meseca kasnije, astigmatizam je iznosio 1,1 dioptriju, a debljina je bila 643 µm u centru i najviše 715 µm na periferiji (slika 5). Oštrina vida ostala je ista. Međutim, godinu dana i dve godine posle operacije, oštrina vida, uz korekciju +1,0 D sfere, bila je 0,8+.

**Sl. 4 – Oko na kome je izvedena trostruka procedura, godinu dana posle operacije**




**Sl. 5 – Topografske i pahimetrijske vrednosti rožnjače dva meseca posle trostruke procedure**

**Diskusija**

Svaki peti slučaj perforativne keratoplastike radi se istovremeno sa operacijom katarakte i ugrađivanjem intraokularnog sočiva [8]. Ovo je razumljivo stoga što katarakta postoji kod mnogih osoba srednjeg i poznog životnog doba kojima je, najčešće zbog Fuksove distrofije ili leukoma rožnjače, indikovana keratoplastika. U svakom od tih slučajeva, potrebno je proceniti koliki udeo u smanjenju oštrine vida ima zamućenje rožnjače, a koliki katarakta, pa plan operacije prilagoditi potrebama i opštem zdravstvenom stanju bolesnika. Ovo nije uvek lako jer nedovoljno providna rožnjača otežava procenu stepena zamućenja sočiva. Oba ova zamućenja utiču na procenu stanja ostalih delova oka, prvenstveno žute mrlje koja, takođe, može da utiče na oštrinu vida. Aparati koji se koriste za određivanja potencijalne oštrine vida, koja bi se dobila posle uspostavljanja providnosti očnih medijuma, u ovakvim slučajevima ne daju bolje rezultate od samog uvida u stanje makule, kada je to moguće [9].

Osnovne prednosti trostruke procedure su: brži oporavak, bolji izgledi za očuvanje endotela rožnjače i niža cena operacije. Glavni nedostatak je nemogućnost tačnog izračunavanja dioptrijske vrednosti intraokularnog sočiva zbog nepoznavanja keratometrijskih vrednosti koje se dobijaju posle perforativne keratoplastike. Ipak, starijim bolesnicima je prihvatljiv brz oporavak sa dobrom, makar i korigovanom, oštrinom vida od dugog čekanja na operaciju katarakte tokom zarastanja i stabilizacije refrakcije posle perforativne keratoplastike. S druge strane, operacija katarakte „pod otvorenim nebom" (kroz veliki centralni otvor u rožnjači) teža je od uobičajene iz dva razloga: prisustva straha od ekspulzivne hemoragije i uklanjanja korteksa iz spljoštene kapsulne vrećice.

Sama perforativna keratoplastika ima nekoliko mana, uprkos tome što i posle sto godina, zbog idealne providnosti kalema i širine indikacija, predstavlja standard u oblasti transplantacije rožnjače. Poremećaji površine rožnjače zbog denervacije i sutura, neretko veliki nepravilan astigmatizam i slabost ožiljka na mestu trepanacije utiču na to da metod izbora u određenim indikacijama bude DSEK. Te indikacije su pseudofakna bulozna keratopatija, Fuksova distrofija rožnjače i *cornea guttata* u slučaju kada je, posle operacije katarakte u drugom oku, ostao hronični edem rožnjače.

U našem slučaju, *cornea guttata*, laki edem strome i debljina rožnjače od 603 μm ukazivali su na značajnu verovatnoću razvoja hroničnog edema rožnjače posle operacije katarakte. Procenjeno je i da bi sama katarakta smanjila vid na oko 0,2. Nekontaktnom biomikroskopijom videlo se da je retina na mestu i da nema grubih promena u makuli. Ovim su postavljene prihvatljive indikacije za trostruku proceduru. Štaviše, površina rožnjače bila je glatka, tako da je keratometrija omogućila pouzdanu kalkulaciju dioptrijske vrednosti implanta. Njena vrednost nije se značajno promenila, tako da glavna prednost odvojenih procedura, pouzdana kalkulacija dioptrijske vrednosti intraokularnog sočiva, nije izgubljena ni prilikom kombinovane operacije.

Dobro prijanjanje kalema omogućeno je istiskivanjem zaostale tečnosti sa IF,[10] kao i dužim prisustvom bule vazduha, omogućenim infuzijom manitola [11].

Osnovna mana svih lamelarnih transplantacija rožnjače je nešto manja oštrina vida nego posle perforativne keratoplastike. Ona nastaje rasipanjem svetlosti na IF koja je ranije pripisivana stvaranju supkliničkog fibroznog ožiljka. Međutim, zaceljenje rane posle EK teče bez pojave fibroznih ćelija [12]. Štaviše, posle početnog brzog oporavka i postizanja oštrine vida od 0,5 kao što je bilo i u našem slučaju, dolazi do vrlo sporog, višemesečnog procesa poboljšanja oštrine vida koji se pripisuje remodelovanju rožnjače praćenom smanjenjem koncentracije proteina iz keratocita koji dovode do rasipanja svetlosti [13].

## Zaključak

Nova trostruka procedura, istovremena fakoemulzifikacija, implantacija sočiva i endotelna keratoplastika, dala je dobar rezultat u pogledu brzine oporavka, oštrine vida i pouzdanosti izračunavanja dioptrijske vrednosti intraokularnog sočiva. Kod Fuksove distrofije rožnjače udružene sa kataraktom, ona ima prednosti i nad odvojenim operacijama, kao i nad istovremenom perforativnom keratoplastikom i operacijom katarakte.

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Primljen 12. I 2010.
Prihvaćen 22. III 2010.

P R I K A Z S L U Č A J A

UDC: 616.711-006-089:[617.3:616.8-089
DOI:10.2298/VSP1109804S

# Sakralni gigantocelularni tumor lečen kompletnom sakrektomijom i spinopelvičnom fiksacijom

## Sacral gigantocellular tumor treated with total sacrectomy and spinal-pelvic fixation

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**Apstrakt**

**Uvod.** Kompletna sakrektomija sa spinopelvičnom fiksacijom uspešan je način radikalnog hirurškog lečenja velikih sakralnih tumora, ali je tehnički veoma zahtevan, te se retko objavljuje u literaturi. Prikazan je bolesnik sa gigantocelularnim tumorom sakruma, uspešno lečen ovom metodom, kod koga su primenjena izvesna poboljšanja standardne operativne tehnike. **Prikaz bolesnika.** Bolesniku starom 30 godina, sa izrazitim bolnim sindromom i sfinkternim smetnjama, dokazan je gigantocelularni tumor koji je zahvatio veći deo sakruma. Operisan je u dva akta. U prvom aktu učinjena je disekcija tumora od retroperitonelanih organa (kolona i krvnih sudova), otvoreni su sakroilijačni zglobovi sa ventralne strane, uklonjen diskus L5 i presečeni korenovi S2–S5. U drugom aktu, učinjenom nakon tri nedelje, dovršena je sakrektomija i učinjena rekonstrukcija karličnog prstena i spinopelvična fiksacija. Tom prilikom modifikovana je standardna tehnika u cilju obezbeđivanja dodatne spinalne fiksacije. Rezultati operacije (trajanje, gubitak krvi, postoperativni deficit) sasvim su komparabilni, a u nekim aspektima i bolji, nego rezultati publikovani u literaturni. **Zaključak.** Sakrektomija sa spinopelvičnom fiksacijom može biti terapija izbora za bolesnike sa ekstenzivnim sakralnim tumorom, ali zahteva multidisciplinarni pristup i značajno iskustvo u instrumentalnoj spinalnoj stabilizaciji.

**Ključne reči:**
**neurohirurške procedure; sakrum; neoplazme, gigantocelularne; lečenje, ishod.**

**Abstract**

**Background.** Total sacrectomy with spinal-pelvic fixation is considered to be a successful approach to the radical surgical treatment of extensive sacral tumors, however, technically very demanding, thus only rarely reported in the literature. We presented a patient with sacral gigantocellular tumor managed successfully using this method but with certain standard operative techniques improvements. **Case report.** A 30-year old patient with a pronounced painful syndrome and sphincter disorders was confirmed to have sacral gigantocellular tumor affecting a greater part of the sacrum. Tumor resection was performed in the first act out off retroperitoneal organs (colon and blood vesels), sacroiliac joints were open by the ventral side, the L5 discus removed, the S2–S5 roots cut off. In the second act, performed three weeks later, sacrectomy was completed by the reconstruction of pelvic ring and spinal-pelvic fixation. Then, the standard technique was modified to provide additional spinal fixation. The results of the operation (duration, blood loss, postoperative deficit) were quite comparable with, and in some aspects even better than the results published in the literature. **Conclusion.** Total sacrectomy with spinal-pelvic fixation can be a therapy of choice in patients with extensive sacral tumors requaring, however, the multidisciplinary approach and a considerable experience with instrumental spinal stabilization.

**Key words:**
**neurosurgical procedures; sacrum; giant cell tumors; treatment outcome.**

### Uvod

Radikalna sakrektomija je idealni način lečenja nekih primarnih sakralnih tumora, ali se ona retko primenjuje, zbog mogućnosti postoperativnog neurološkog deficita i neophodnosti komplikovane postoperativne rekonstrukcije spinopelvičnog spoja [1]. Najpodesniji tumori za ovu vrstu hiruškog lečenja su gigantocelularni tumori i tumori niskog stepna malignoteta (hordomi, hordosarkomi), dakle, tumori koji daju lokalne simptome, ali imaju mali potencijal metastaziranja i neosetljivi su na druge vidove onkološkog lečenja (hemioterapija, radioterapija) [2].

Nakon ovakvih operacija primenjuju se različite metode spinopelvične fiksacije, u cilju stabilizacije i fuzije u tranzitnoj zoni između kičme i karlice. Neophodno je da se zadovolje i anatomski i biomehanički zahtevi, odnosno da se us-

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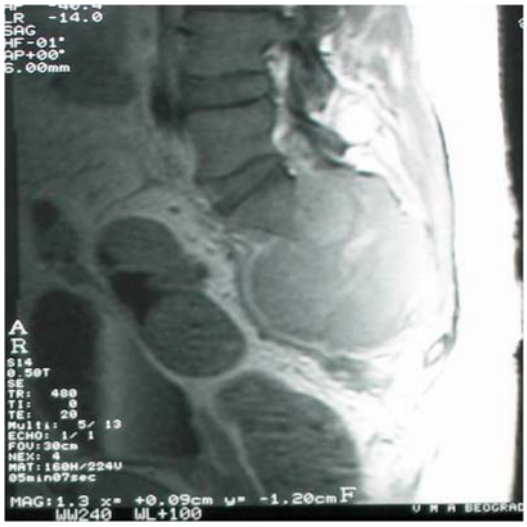
postavi solidna fuzija koja bi izdržala veliki pritisak gornjih delova tela, a u isto vreme da se obezbedi dovoljna pokretljivost lumbosakralne regije [3]. Allen i Ferguson [4] opisali su originalnu metodu lumboilijačne fiksacije šipkom u obliku slova „L“, koja je postala poznata kao Gelveston tehnika fiksacije karlice, a Jackson i Gokaslan [5] modifikovali su ovu tehniku i primenili je na rešavanje spinopelvične nestabilnosti, nastale nakon operacija lumbosakralnih tumora.

U radu je prikazan bolesnik sa gigantocelularnim tumorom sakruma, kod kojeg je uspešno učinjena kompletna resekcija sakruma, a, potom, spinopelvični defekt rekonstruisan i fiksiran Galveston tehnikom, delimično modifikovanom postavljanjem dodatne šipke i na spoljašnju stranu karličnog prstena.

**Prikaz bolesmika**

Mučkarac, star 30 godina, javio se na pregled u junu 2002. godine, zbog jakog bola u krstima sa širenjem u obe noge do stopala i trnjenja u stopalima. Tegobe su se javile oko šest meseci pre prvog pregleda. Vremenom, bol je postajao nepodnošljiv, javila se perinealna utrnutost, opstipacija i urinarna inkontinencija. U neurološkom nalazu dominirala je slabost plantarne fleksije oba stopala, ugašeni Ahilovi refleksi i ispad senzibiliteta u perianalnoj regiji, perineumu i sa zadnje strane obe natkolenice.

Nalaz magnetne rezonance (MR) kičmenog stuba ukazao je na postojanje velikog tumora koji je zahvatio sakrum od S2 do S5 i širio se u oba krila sakralne kosti, ali bez zahvatanja sakrolijačnih zglobova (slika 1). Potvrđena je kompletna opstrukcija sakralnog kanala distalno od S1, sa zahvatanjem sakralnih lamina i širenjem tumora dorzalno u meka tkiva i ventralno, kroz prednji korteks sakruma u malu karlicu. U septembru 2002. godine učinjena je otvorena biopsija tumora kojom je dokazano da se radi o primarnom, malignom gigantocelularnom tumoru. Mesec dana nakon biopsije tumora, a uz neurološki nalaz i subjektivne smetnje slične kao i pri inicijalnom pregledu, urađena je kompletna resekcija sakruma sa spinoplevičnom fiksacijom. Operacija je urađena u dva akta, u razmaku od 21 dan. Operacija je ukupno trajala 26 sati, računajući oba akta, uz gubitak krvi od 24 litra.




**Sl. 1 – Preoperativni nalaz magnetne rezonance (MR) lumbosakralne kičme bolesnika sa gigantocelularnim tumorom sakruma**

*Prvi operativni akt*

Učinjena je medijalna laparatomija i retroperitonelnim pristupom eksplorisana je prednja strana lumbosakralne regije. Mobilisani su visceralni organi i odvojeni od ventralne strane pršljena L5 i sakruma. Retrosigmoidni kolon odvojen je od presakralne fascije do vrha kocigealne kosti, unutrašnja ilijačna arterija i vena podvezane su i presečene, kao i medijalni sakralni krvni sudovi. Nakon njihovog presecanja jasno su se prikazali nervni korenovi S1 i S2 obostrano. Sakrilijačni zglobovi identifikovani su lateralno od ovih nervnih struktura i potom je učinjena obostrana sakrilijačna osteotomija radi otvaranja sakrilijačnog zgloba sa ventralne strane. Disk L5 uklonjen je kompletno sa prednjim i bočnim delom anulusa fibrizusa. Periost koji nije bio zahvaćen tumorom koagulisan je, a sakralni nervni korenovi S2–S5 presečeni su ventralno od lumbalnog stabla, a pre ulaska u tumor. Tokom operacije tumor je odvojen od krvnih sudova sa prednje strane, nervnih korenova i od visceralnih struktura, a kičmeni stub i sakralna kost odvojeni su u ventralnom delu od sakruma, odnosno od ilijačnih kostiju.

*Drugi operativni akt*

Nakon 21-og dana, po zarastanju prve rane i oporavka od značajnog intraoperativnog gubitka krvi, učinjen je drugi akt operacije. Bolesnik je postavljen u položaj ventralnog dekubitusa, kroz medijalnu inciziju podignut je lumbosakralni mišićni flap od sakruma i retrahovan lateralno i kaudalno. Na ovaj način omogućena je dobra vizuelizacija lateralno, iza sakroilijačnih zglobova i kaudalno, do kocigealne kosti, a kranijalno do L3 spinoznog nastavka. Prikazali su se poprečni nastavci pršljenova L3–L5, učinjena je široka laminektominja L5 i prikazani su duralna vreća i odgovarajući nervni korenovi kaude ekvine. Duralna vreća je podvezna duplim šavom i presečena ispod ishodišta S1 nervnog korena. Nakon odvajanja duralne vreće, jasno se prikazao, a potom i uklonio dorzalni deo međupršljenskog diskusa L5, koji je u prvom aktu sa prednje i bočne strane reseciran. Na ovaj način kičmeni stub odvojen je kompletno od karlice. Bilateralnom osteotomijom krila sakralne kosti paralelno sa sakroilijačnim zglobovima kompletirano je presecanje i odvajanje sakruma od ilijačnih kostiju započeto sa prednje strane u prvom aktu. Sakrum je delimično mobilisan i bilo je moguće da se identifikuju sakrospinozni i sakrotuberozni ligamenti koji su presečeni. Rektum je odvojen od distalnog sakrokokcigealnog pripoja. Sakralni nervni korenovi, S2–S5 presečeni su na njihovom izlasku iz sakruma uz čuvanje išijadičnog nerva od oštećenja. Potom je izvađen kompletan sakrum sa tumorom u jednom komadu.

*Spinopelvična fiksacija*

Kičmeni stub ostao je kompletno odvojen od karlice. Postavljeni su transpedikularni, poliaksijalni šrafovi od L3 do L5. Za šrafove fiksirane su dve vertikalne šipke koje su

oblikovane prema Galveston tehnici i distalno fiksirane u ilijačne kosti između dva korteksa. Dva poprečna konektora iskorišćena su za povezivanje vertikalnih šipki. Deo tibijalne kosti kao autograft, uzet sa desne noge, iskorišćen ja za zatvaranje prostora između dve ilijačne kosti, kako bi sprečio zatvaranje i kolaps karličnog prstena. Ovaj autograft je za karlične kosti fiksiran sa dva transilijačna šrafa. Da bi se preveniralo otvaranje karličnog prstena, odnosno razmicanje ilijačnih kostiju, primenjena je modifikacija originalne metode postavljanjem šipke u obliku slova P, koja je sa spoljašnje strane obuhvatila ilijačne kosti i za njih fiksirana šrafovima. Autologni graftovi uzeti sa zadnje ilijačne kriste, postavljeni su u prazan prostor između ilijačnih kostiju i donje površine pršljenskog tela L5, zajedno sa koštanim alograftovima i sa autolognim graftovima lamine L5, a sa ciljem da se uspostavi solidna koštana fuzija u spinopelvičnom prostoru. Prethodno mobilisani lumbosakralni mišićni flap postavljen je da zatvori prazan prostor iznad koštanih graftova. Koža je ušivena direktno, bez dodatnih, kožnih rasteretnih incizija i bez dodatnih koštanih režnjeva.

**Sl. 2 – Postoperativni radiografski (Rtg) snimak karlice i lumbosakralne kičme u anterioposteriornoj (AP) projekciji: stanje nakon sakrektomije uz adekvatnu spinopelvičnu fiksaciju sedam godina nakon operacije - potpuno koštano srastanje karlice i kičme**

*Postoperativni tok*

Aspiraciona drenaža operativne rane provedena je u naredna tri dana. Bolesnik je mirovao u krevetu osam nedelja, pre nego što je započeta mobilizacija sa sedenjem i fizikalna terapija u krevetu. Postoperativno, u neurološkom nalazu ostala je slabost dorzalne fleksije stopala, koja se vremenom, uz fizikalnu terapiju, značajno oporavila. Uz fizikalnu terapiju, započet je trening mokraćne bešike zbog inkontinencije, a opstipacija je tretirana odgovarajućom dijetom sa laksativima i klizmama. Neurogena bešika je, u nastavku rehabilitacije tretirana intermitentnim kateterizacijama. Kontrola mikcije i defekacije bila je oštećena zbog obostranog presecanja korenova S2, ali doslednom dijetom i kateterizacijom, ove funkcije su uspostavljene na zadovoljavajućem nivou. Preoperativno ispoljen, nepodnošljivi bolni sindrom, u potpunosti je bio saniran. Fizikalni banjski tretman bio je provođen narednih šest meseci, posle čega je došlo do stabilizacije sfinkterijalnih tegoba i mogućnosti samostalnog hoda, bez pomagala. Godinu dana nakon operacije bolesnik se vratio na prethodni posao i bio je osposobljen da samostalno upravlja motornim vozilom, bez ikakve adaptacije. Kontrolni rendgenogram učinjen dvanaest meseci nakon operacije, pokazao je potpunu koštanu fuziju u spinopelvičnoj regiji, sa očuvanim sagitalnim balansom kičmenog stuba (slika 2). Sedam godina nakon operacije, bolesnik je bez bolova, bez radioloških znakova recidiva tumora, radno sposoban i uključen u svakodnevne životne aktivnosti (slika 3).

**Sl. 3 – Izgled bolesnika sedam godina nakon operacije, sposobnog da samostalno hoda i vozi auto**

## Diskusija

Dok suptotalna resekcija sakruma, kaudalno od sredine S1 pršljenskog tela, ne destabilizuje karlicu, totalna sakrektomija zahteva obostrano povezivanje lumbalnog dela kičmenog stuba sa ilijačnim kostima, kao i rekonstrukciju zadnjeg dela karličnog prstena [6]. Totalna sakrektomija se retko izvodi zbog dva razloga: najpre, zbog toga što je ova operacija kompleksna i zahteva znanje iz različitih oblasti hirurgije

(neurohirurgija, abdominalna hirurgija, ortopedija, plastična hirurgija), a, drugo, zato što zahteva svesno žrtvovanje nekih nervnih struktura kako bi se postigao potpuni radikalitet [7].

Očuvanje lumbalnih nervnih korenova neophodno je kako bi se spasila motorna inervacija nogu, seksualne funkcije i kontrola mokrenja i defekacije. Svesno žrtvovanje sakralnih nervnih korenova je u funkciji trajnog izlečenja i efikasnog odstranjenja malignog tumora, posebno što se neurološki deficit, uzrokovan njihovim presecanjem, može efikasno popraviti postoperativnom rehabilitacijom [8].

Među prvima, totalnu sakrektomiju prikazali su Edvards [9] i Michel [10], ali oni nisu pridavali značaj rekonstrukciji karličnog prstena ili spajanju kičme i karlice. Mi smatramo da je rekonstrukcija nakon totalne sakrektomije neophodna, kako bi se uspostavila stabilnost koja omogućava brže postizanje samostalnog hoda tokom postoperativne rehabilitacije i, samim tim, uključenje u uobičajene dnevne aktivnosti.

Trenutno, u primeni su različiti metodi lumbosakralne fiksacije koji se mogu klasifikovati u dve osnovne kategorije: tehnike koje koriste sublaminarne implantate i ilijačne šipke i tehnike fiksacije šrafovima. Sublaminarni implantati (kuke, žice ili kablovi) postižu samo dorzalnu krutu vezu, koja onemogućava pokrete fleksije [11]. Ovi implantati ne omogućavaju dovoljnu torzionu stabilnost ili otpornost na ekstenziju, tako da je stepen fuzije sličan kao kod bolesnika koji su operisani bez dodatne instrumentacije. Pseudoartroza je čest problem kod ovih bolesnika. Zato je napravljena modifikacija goreopisane tehnike, koju su inicijalno opisali Allen i Ferguson [4]. Modifikacija podrazumeva upotrebu transpedikularnih šrafova vezanih za šipku koja se kaudalno plasira u ilijačne kosti u dubini 8–9 cm [1]. Različitim tehnikama instrumentacije primenjivanim u spinopelvičnoj rekonstrukciji, a nakon totalne sakrektomije, težilo se postizanju izvesnog napretka, pre svega u biomehaničkom smislu. Tako, opisuje se upotreba sakralne šipke, koja povezuje ilijačne kosti i vezuje se za kičmu, sa Haringtonovom šipkom i laminarnim kukama [12], zatim upotreba Cotorel-Dubousset šipke i laminarnih kuka sa sakralnom šipkom ili AO pločicom [6, 13], upotreba transpedikularnih šrafova sa ilijačnim šrafovima vezanim za pločice [8, 14] i upotreba vertikalne Galveston šipke povezane sa poprečnim spinalnim šipkama i transpedikularnim šrafovima [14, 15].

Čak i skorije objavljeni radovi ne pridaju značaj postavljanju koštanih graftova kao dodatak instrumentaciji čiji je cilj da obezbede dodatnu unutrašnju, spinalnu fiksaciju [16]. Nekorišćenje transverzalne, transilijačne šipke omogućava da se ilijačne kosti koje su otvorene i nefiksirane sa zadnje strane, razdvoje lateralno i anteriorno prema, popularno nazvanom, principu „otvorene knjige“. Primenjena modifikovana Galveston tehnika za rekonstrukciju nakon totalne sakrektomije predstavlja unapređenje svih ranije navedenih tehnika [17]. Svaka Galveston šipka formira jedinstven most između lumbalnog dela kičme i ilijačne kosti, a transilijačna šipka kompletira i zatvara, operacijom otvoren, karlični prsten. Dodatno učvršćen autolognim i alogenim koštanim graftom, ovaj sistem instrumentacije onemogućava podjednako kaudalnu migraciju i aksijalnu rotaciju kičmenog stuba, uz istovremeno onemogućavanje fenomena „otvorene knjige“. upotrebom transilijačne krute šipke [18, 19]. Zbog dodatnog pojačanja i prevencije otvaranja karličnog prstena, upotrebili smo još jednu šipku u obliku širokog slova P koja ilijačne kosti spaja sa spoljašne strane i za njih se fiksira transkortikalnim ilijačnim šrafovima. Ovakav sistem omogućava stabilnost kičmenog stuba u sagitalnoj ravni, a, takođe, onemogućava rotaciju oko aksijalne linije.

U dostupnoj literaturi postoje podaci o samo devet bolesnika kod kojih je učinjena totalna sakrektomija, a podaci o dužini operacije, količini izgubljene krvi i ishodu uporedno su prikazani u tabeli 1. Gubitak krvi može biti izuzetno veliki: od 6,5 L za operacije rađene u jednoj fazi ili 10,1 L za operacije rađene u dve faze [13, 14] do, čak, 80 L [10]. Gubitak krvi kod našeg bolesnika bio je nešto veći nego što je objavljeno za dvofazne operacije i iznosio je 26 L, približno količini koju je prikazao Gokaslan i sar. (21,5 L) [1]. Ukupno vreme operacije (26 h) bilo je, približno jednako dužini operacije koju su objavili Michel [10] i Shikata i sar. [12], ali je kraće od onoga koje su objavili Gokaslan i sar. (34,2 h) [1]. Od prikazanih devet bolesnika u ta-

**Tabela 1**

**Uporedni prikaz podataka iz literature vezanih za trajanje operacije, gubitak krvi i ishod lečenja kod kompletne resekcije sakruma**

| Autor i godina | Uzrast (god), pol (M/Ž) | Broj operativnih aktova | Ukupno operativno vreme (h) | Ukupni gubitak krvi (L) | Ishod |
|---|---|---|---|---|---|
| Michel A, 1990 [10] | 27, M | 2 | 20 | 80 | Hod uz 2 potkolenične ortoze i 2 štapa (2 godine) |
| Shikata J et al.,1988 [12] | 34, M | 3 | 26 | 8,3 | Hod uz mider i štap; više u kolicima (2,1 godina) |
| Santi MD et al.,1993 [14] | 48, M | 1 | 18 | 6,5 | Hod uz obostranu dinamičku ortozu (2,7 godina) |
| Blatter G et al.,1994 [20] | 43, M | 1 | – | 40 | Hod uz pilot lift do 30 min. (2 godine) |
| Jackson Z et al., 2000 [5] | 37, Ž | 2 | 34,2 | 21,5 | Hod sa štapom (1 godina) |
| | 30, Ž | 2 | 34 | 21,7 | Normalan hod, vožnja auta (1 godina) |
| Zhang HY et al., 2003 [13] | 32, M | 2 | 23 | 10,1 | Normalan hod (6 meseci) |
| GalliaGL et al., 2005 [3] | 36, Ž | 1 | 10 | 7,5 | Hod sa štapom (10 meseci) |
| Newman C et al., 2008 [17] | 38, M | 2 | 13 | 13 | Normalan hod (1 godina) |
| Savić M (prezentovana publikacija) | 30, M | 2 | 26 | 26,5 | Normalan hod, vožnja auta (1 godina) |

beli 1, tri bolesnika su, nakon totalne sakrektomije, mogla da hodaju bez pomagala, a jedan i da vozi auto (dva bolesnika nakon jedne godine, a jedan nakon šest meseci). Druga dva bolesnika mogla su da hodaju uz pomoć štapa, jedan nakon jedne godine, a drugi nakon deset meseci posle operacije. Svih pet bolesnika bilo je starosti oko 30 godina, što može biti razlog za kraći rehabilitacioni period i za bolji neurološki ishod opisane hirurške tehnike. Bolesnik koga smo prikazali hodao je bez pomoći štapa godinu dana nakon operacije, što se može pripisati pravilno odabranoj i adekvatno primenjenoj hirurškoj tehnici, ali i mlađem životnom dobu.

**Zaključak**

Totalna sakrektomija sa spinopelvičnom rekonstrukcijom može biti efikasna operacija za primarno maligne tumore koji zahvataju sakrum, bez širenja na susedne koštane strukture. Pri tome, tehnika rekonstrukcije i fiksacije između lumbalne kičme i ilijačnih kostiju sistemom transpedikulkarnih šrafova i šipki (modifikovana tehnika Galveston) sa dodatkom šipke sa zadnje strane ilijačnih kostiju omogućava adekvatnu stabilizaciju dovoljnu za samostalnu pokretljivost.

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Primljen 12. I 2010.
Prihvaćen 21. IV 2010.

P R I K A Z S L U Č A J A

UDC: 616.831-006-07:616.89-008-079.4
DOI:10.2298/VSP1109809I

# Tumori mozga kod bolesnika koji su primarno psihijatrijski lečeni

## Brain tumors in patients primarly treated psychiatrically

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**Apstrakt**

**Uvod.** Psihijatrijski simptomi nisu retke kliničke manifestacije tumora mozga. Tumori mozga koji se manifestuju simptomima povišenog intrakranijalnog pritiska, fokalnim neurološkim znacima i konvulzijama, obično se dijagnostikuju rutinskim dijagnostičkim procedurama od strane neurologa, ili ređe, neurohirurga. Međutim, kod „neurološki nemih" tumora, kada se psihijatrijski simptomi javljaju kao prvi znak tumora mozga, bolesnici se upućuju psihijatru koji se bavi lečenjem psihičkih smetnji, zbog čega tumori ostaju dugo nedijagnostikovani. **Prikaz bolesnika.** U radu su prikazana tri bolesnika sa dijagnostikovanim moždanim tumorom, koji su primarno bili upućeni psihijatru na lečenje zbog psihičkih smetnji, dok je neurološki nalaz kod sva tri bolesnika bio bez fokalnih ispada i povišenog intrakranijalnog pritiska. Kompjuterizovanom tomografijom (KT) kod bolesnika sa opsesivno-kompulzivnim poremećajem i suicidalnim idejama detektovan je tumor u predelu desne insule; kod bolesnika sa paranoidnodepresivnom simptomatologijom ustanovljen je tumor u desnom parijetotemporalnom delu mozga, dok je kod bolesnika sa alkoholizmom ustanovljen tumor u levom frontalnom predelu. **Zaključak.** Psihijatrijski simptomi/poremećaji kod tumora mozga nisu dovoljno specifični i mogu imati istovetnu kliničku prezentaciju kao i funkcionalni psihijatrijski poremećaji, posebno u slučajevima „neurološki nemih" tumora mozga. Zbog toga, kod bolesnika sa naglim početkom psihijatrijskih simptoma, kod pacijenata sa neočekivanim promenama u mentalnom statusu ili kod iznenadne pojave glavobolje, kao i kod terapijski-rezistentnih psihijatrijskih poremećaja, uvek treba imati u vidu i mogućnost udruženog postojanja tumora mozga.

**Ključne reči:**
**mozak, neoplazme; mentalni poremećaji; znaci i simptomi; dijagnoza; dijagnostičke greške; lečenje, ishod.**

**Abstract**

**Introduction.** Psychiatric symptoms are not rare manifestations of brain tumors. Brain tumors presented by symptoms of raised intracranial pressure, focal neurological signs, or convulsions are usually first seen by the neurologist or less frequently by the neurosurgeon in routine diagnostic procedures. On the other hand, when psychiatric symptoms are the first manifestation in "neurologically silent" brain tumors, the patients are sent to the psychiatrist for the treatment of psychiatric symptoms and brain tumors are left misdiagnosed for a long period of time. **Case Report.** We presented three patients with the diagnosed brain tumor where psychiatrist had been the first specialist to be consulted. In all three cases neurological examination was generally unremarkable with no focal signs or features of raised intracranial pressure. CT scan demonstrated right insular tumor in a female patient with obsessive-compulsive disorder (OCD); right parietal temporal tumor in a patient with delusions and depression and left frontal tumor in a patient with history of alcohol dependency. **Conclusion.** Psychiatric symptoms/disorders in patients with brain tumors are not specific enough and can have the same clinical presentation as the genuine psychiatric disorder. Therefore, we emphasize the consideration of neuroimaging in patients with abrupt beginning of psychiatric symptoms, in those with a change in mental status, or when headaches suddenly appear or in cases of treatment resistant psychiatric disorders regardless the lack of neurological symptoms.

**Key words:**
**brain neoplasms; mental disorders; signs and symptoms; diagnosis; diagnosic errors; treatment outcome.**

### Uvod

Psihijatrijski simptomi nisu retke kliničke manifestacije tumora mozga [1–5]. Prema nekim analizama čak polovina bolesnika sa tumorom mozga pokazuje i neku psihijatrijsku simptomatologiju [6]. Sa druge strane, samo kod 18% bolesnika psihijatrijski simptomi su inicijalna manifestacija moždanog tumora [1, 7]. U tim slučajevima, najčeš-

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će su u pitanju izmene ličnosti, emocionalne promene ili intelektualni deficit [8, 3]. Neretko, kao prezentujući simptomi tumora mozga sreću se psihotični simptomi i panični napadi [3].

Vrsta i težina psihopatoloških manifestacija zavisi i od lokalizacije tumora [9]. Tumori frontalnog lobusa mogu dovesti do promena ličnosti (dezinhibicije, iritabilnosti, oštećenja rasuđivanja, abulije), dok se manična slika javlja kod tumora ventralne aree desne hemisfere [10]. Frontalni tumori desne hemisfere češće daju pseudoeuforičnu sliku, dok tumori leve hemisfere češće daju kognitivne smetnje, pseudodepresivni afekt, abuliju i akineziju [11]. Vizuospacijalna inkordinacija uočava se kod tumora desne hemisfere [12] za razliku od tumora leve hemisfere koji se prezentuju afazijom i mentalnim smetnjama tipa apatije, indiferentnosti i psihomotorne retardacije [11]. Tumori parijetalnog lobusa ređe su udruženi sa psihijatrijskim simptomima [6].

Ne samo da psihopatologiju oblikuje lokalizacija [9, 13], nego i brzina rasta i agresivnost tumora daju specifične psihopatološke fenomene. Tako se kod bolesnika sa tumorima visokog stepena maligniteta pojavljuju psihološki poremećaji sa naglim početkom kao što su anksiozni i panični poremećaj [14], za razliku od bolesnika sa tumorima niskog stepena maligniteta kod kojih se najčešće sreću epileptični poremećaji [15].

Stručna javnost je saglasna da moždani tumori mogu da budu uzrok različite psihopatologije kao i da pojava pojedinih psihijatrijskih entiteta najčešće koreliše sa lokalizacijom i lateralizacijom neoplazije. Međutim, u dostupnoj literaturi relativno je malo prikaza pojedinačnih psihijatrijskih entiteta koji se na osnovu kliničke slike mogu izdvojiti kao entitet *per se* i pojedinih tumora mozga [1].

Tumori mozga koji se manifestuju simptomima povišenog intrakranijalnog pritiska, fokalnim neurološkim znacima i konvulzijama, obično su u rutinskim dijagnostičkim procedurama dijagnostikovani od strane neurologa, ili ređe, neurohirurga [2]. Sa druge strane, u slučajevima "neurološki nemih" tumora, kada se psihijatrijski simptomi jave kao prvi znak tumora mozga, bolesnici bivaju upućeni psihijatru koji leči psihičke smetnje, te tumori mogu dugo da ostanu nedijagnostikovani. Tek u slučaju dijagnostičkih ili terapijskih nejasnoća [16], bolesnici sa tumorom mozga koji ispoljavaju psihijatrijsko oboljenje naknadno se upućuju na dodatna neurosnimanja, kada se tumor i dijagnostikuje [17].

Cilj rada je bio da se kroz prikaz tri dijagnostički različita slučaja bolesnika sa tumorom mozga ukaže da prezentujuća psihijatrijska simptomatologija može biti posledica prisustva i „neurološki nemih tumora".

U radu su prikazana tri bolesnika kod kojih je utvrđeno postojanje moždanog tumora, a koji su primarno upućeni psihijatru na lečenje zbog opsesivno-kompulzivnog poremećaja (OKP) sa suicidnim idejama, paranoidno-depresivnog ispoljavanja i alkoholizma.

**Prikaz bolesnika**

Kod prve bolesnice, stare 33 godine, dve i po godine pre hospitalizacije prvi put su se javile prisilne misli i kompulzivne radnje, kao i suicidne ideje. Premorbidno, postojale su izražene opsesivne crte ličnosti. Prisilne misli odnosile su se na anticipaciju da će nekome nešto strašno da se desi, a od njih se branila prsilnim radnjama kao što su uključivanje i isključivanje svetla; zatvaranje i otvaranje slavine; pranje i ispiranje veša („Jednu košulju može da pere od podne do večeri", prema rečima supruga); rituali pri ulasku u krevet – brojanje koraka, vraćanje, ponovno brojanje, ustajanje, sedanje na krevet. Repertoar prisilnih misli i kompulzivnih radnji vremenom se širio i sve više uticao na svakodnevno funkcionisanje. Bila je bez podataka o hereditarnom opterećenju.

Bolesnica je lečena ambulantno primenom različitih antidepresiva: tricikličnih antidepresiva i selektivnih inhibitora ponovnog preuzimanja serotonina (SSRI). Tokom dve i po godine ambulantnog lečenja neurološki pregled je tri puta ponavljan i uvek je bio u potpunosti uredan. Budući da se u ambulantnom tretmanu nije dobio pozitivan terapijsku odgovor, a bolesnica je sve teže funkcionisala, doneta je odluka o hospitalizaciji.

Prilikom prijema bolesnica je bila svesna, ispravno orijentisana u svim modalitetima. Verbalni kontakt se lako uspostavljao, održavao i produbljivao. Na postavljena pitanja davala je direktne i logične odgovore. Bile su očuvane sposobnosti usmeravanja i održavanja pažnje, bez prisustva perceptivnih obmana. Nisu bili prisutni formalni poremećaji mišljenja, ali u sadržaju mišljenja postojao je širok repertoar prisilnih misli i kompulzija – višesatno pranje ruku, dominantno; u bolničkim uslovima, opserivarni su kompulzivni rituali pri ulasku u krevet. Bolesnica je bila visokoanksiozna, napeta, nije krila nelagodnost. Osnovni afektivni ton bio je subdepresivan. Voljna aktivnost bila je kompromitovana prisutnim prisilnim mislima i kompulzivnim radnjama. Nagonski dinamizmi bili su sniženi sa verbalizacijom suicidnih ideja.

Po prijemu, bolesnica je navela da ima glavobolje lokalizovane u potiljačnom delu i u vratu („Tako me nekako žari, ne smem da dodirnem glavu"). Glavobolja nije bila praćena mučninom, niti povraćanjem.

Prilikom prijema ustanovljen je plan kliničke obrade. S obzirom na to da je u kliničkoj slici dominirao opsesivno-kompulzivni poremećaj, bolesnici je najpre uvedena peroralna terapija alprazolamom, u dnevnoj dozi od 1,5 mg, sa idejom da se nakon incijalne dijagnostičke obrade, u terapiju uvede i antidepresiv. Kako su rezultati komplementarnih pregleda otkrili sasvim novo oboljenje, kod ove bolesnice nije uveden antidepresiv do kraja hospitalizacije koja je trajala 11 dana.

Neurološkim pregledom na prijemu kod bolesnice je ustanovljena laka asimetrija lica, glava je bila lako povijena na levu stranu, jezik je blago devirao u desno pri protruziji, levi taban bio je nem, bez drugih ispada i deficita u neurološkom nalazu. Osnovne laboratorijske analize bile su u potpunosti uredne. Pregledom očnog dna (FOU), takođe, dobijen je uredan nalaz. Četvrtog dana hospitalizacije urađeno je psihološko testiranje gde su se kod bolesnice pri rešavanju Benton testa javile greške poput iskrivljenja slike i perzeveracije velikih figura.

Elektroencefalografski nalaz (EEG) ukazivao je na iregularnu i mešovitu osnovnu aktivnost – difuzno nespecifično izmenjenu, lakog stepena. Iznad desne hemisfere parijeto temporalno registrovana je diskontinuirana nespecifična theta hipersinhronija u toku hiperventilacije, nakon čega je hitno zakazano neurosnimanje. Kako u tom trenutku u ustanovi u kojoj je bolesnica lečena nije bila dostupna neinvazivna metoda pregleda, zbog jednostranog nalaza na EEG, kod ove bolesnice urađena je angiografija. Desna karotidna angiografija pokazala je da su kontrastom prebojeni krvni sudovi: grane desne unutrašnje karotidne arterije; stablo desne arterije cerebri medije lučno dislocirani kaudo-anteriorno. Periferna arborizacija označenog stabla bila je uredna i prohodna.

Bolesnica je upućena na Neurohiruršku kliniku u Beogradu gde je urađena kompjuterizovana tomografija (KT) mozga i u predelu desne insule ustanovljena je nehomogena hiperdenzna formacija veličine 2,5 × 2,2 cm, bez perifernog edema i kompresivnog efekta. Homogeno se prebojavala po davanju intravenskog kontrasta. Neurohirurška intervencija nije obavljena zbog inoperabilnosti tumora prema proceni neurohirurga – „operacija nije indikovana zbog rizika od nastanka trajnog neurološkog deficita“. Bolesnica je naredne godine po prvi put imala epileptični napad. Epileptični napadi su se ponavljali uprkos primenjenoj terapiji. Tokom šest godina lečenja, promenjeno je više anitepileptika (karbamazepin, lamotrigin, fenobarbiton, gabapentin). Nakon što je kod bolesnice došlo do ozbiljanog neželjenog događaja prilikom uvođenja lamotrigina u terapiju (Stevens Johnson sindrom – *Necrolysis epidermalis toxica*), zbog čega je bolesnica bila i vitalno ugrožena, potpuno je prestala da dolazi na kontrolne preglede i da koristi medikamentnu terapiju. Dugo je odbijala da napravi bilo kakav kontakt sa osobljem bolnice u kojoj je prvi put lečena. U telefonskom razgovoru pre više od godinu dana, od bolesnice smo saznali da su prisilne misli i kompulzivni rituali i dalje vrlo izraženi, da praktično ne izlazi iz sobe, ali da predložene preglede i terapiju odbija.

Drugi bolesnik, star 48 godina, dva meseca pre hospitalizacije prvi put se javio na psihijatrijski pregled, na nagovor porodice. Osnovne žalbe prilikom prvog pregleda bile su napetost, uznemirenost, razdražljivost, neraspoloženje, teškoće usnivanja i stalna briga. Postojali su brojni strahovi, evidentno je bilo socijalno povlačenje, pasivizacija, gubitak inicijative, „*deja vu*“ fenomeni, sumnjičavost. Nekoliko meseci unazad, prekinuo je kontakt sa susedima jer ga prate, prisluškuju, nije se osećao sigurno u susedstvu u kom živi. Osim toga, bolesnik se žalio na rekurentne glavobolje, posebno u jutarnjim časovima, koje nisu bile praćene mukom, gađenjem, povraćanjem, fotofobijom. U porodičnoj anamnezi nije bilo bolesti od značaja za psihijatrijski hereditet.

Prilikom pregleda na prijemu bolesnik je bio svestan, ali, iako je bio ispravno orjentisan u svim modalitetima, već na prvi pogled delovao je zbunjeno i odsutno. Verbalni kontakt se uspostavljao, održavao, teže produbljivao. Produžena je bila verbalna latenca i kao da se prisećao kod svakog odgovora. Pažnja je bila hipertenacitetna. Bio je usporenog misaonog toka, sa nesistematizovanim sumanutim idejama persekucije, bez perceptivnih obmana. Repertoar afektivnog reagovanja je bio redukovan uz gubitak interesovanja za okolinu, a osnovni afektivni ton bio je depresivan. Bolesnik je bio sniženih voljno nagonskih dinamizama.

Budući da je nivo funkcionisanja bolesnika bitno narušen, doneta je odluka da se on hospitalizuje radi sprovođenja detaljne dijagnostike i opservacije ponašanja na odeljenju. Tokom kratkotrajne hospitalizacije jedina terapija bio je klonazepam u dnevnoj dozi od 2 mg, kao i analgetska terapija zbog stalnih glavobolja koje je naveo nakon prijema u bolnicu.

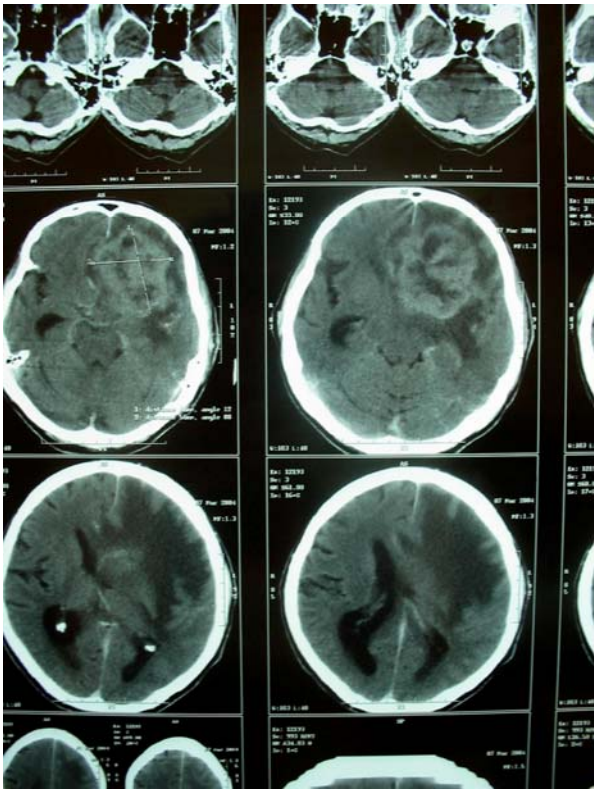
Tokom hospitalizacije osnovne laboratorijske analize bile su uredne, kao i neurološki nalaz. Zbog stalnih glavobolja urađen je oftalmološki pregled koji je ukazao na postojanje staze papile, zbog čega su hitno urađeni EEG (iregularna osnovna aktivnost frekvencije 8–9 cps. bez specifičnih grafoelemenata, nalaz u granicama normale) i KT pregled mozga (supratentorijelno, desno parijetotemporalno i paraventrikularno, ekspanzivna promena dimenzija 80 × 55 × 80 mm). Narednog dana bolesnik je premešten u Kliniku za neurohirurgiju i obavljena je hirurška intervencija. Patohistološki nalaz tumora bio je *Astrocytoma gradus III*. Porodica i bolesnik nisu prihvatili predloženu zračnu postoperativnu terapiju. Bolesnik je egzitirao tri meseca nakon operacije u svojoj kući (slika 1).

**Sl.1 – Nalaz kompjuterizovane tomografije (KT) kod drugog bolesnika: supratentorijalno, desno parijetotemporalno i paraventrikularno, ekspanzivna promena dimenzija 80 × 55 × 80 mm**

Treći bolesnik, star 57 godina upućen je psihijatru od strane interniste. Prilikom internističkog pregleda postavljena je dijagnoza *Hypertensio arterialis*, *Aethilismus*. Bolesnik je bio dugogodišnji potator, ali je zbog izraženih digestivnih tegoba bio u apstinenciji dva meseca pre psihijatrijskog pregleda. Prilikom prvog pregleda žalio se na opštu malaksalost, gubitak apetita, rekurentno povraćanje, otežano uzimanje hrane, teškoće pri hodu i osećaj opšte, mentalne i motorne

usporenosti. Na psihijatrijskom pregledu prilikom prijema bolesnik je bio svestan, sa mogućnošću uspostavljanja verbalnog kontakta, nesigurno temporalno orijentisan, ispravno orijentisan u drugim modalitetima. Odgovore je davao sa latencom. Pažnja mu je bila hipertenacitetna, a misaoni tok je bio usporen, bez prisustva sadržajnih poremećaja mišljenja. Nije bilo perceptivnih obmana. Osnovni afektivni ton bio je subdepresivan, a voljnonagonski dinamizmi sniženi. Neurološki pregled bio je uredan. Od strane neurologa ordinirani su analgetici i piracetam. Psihijatrijska terapija nije uvedena.

Četvrtog dana hospitalizacije naglo je došlo do pogoršanja, bolesnik je postao dezorijentisan, verbalni kontakt se gotovo nije uspostavljao, izrazito je bio psihomotorno usporen. Tokom istog dana, bolesnik je izgubio i kontrolu sfinktera. U ponovljenom neurološkom pregledu Rombergov znak je bio pozitivan, a ostali neurološki nalazi bili su uredni. Istog dana obavljen je i oftalmološki pregled i nalaz na očnom dnu (FOU) opisan je kao uredan. Šestog dana hospitalizacije opisana psihopatologija perzistirala je i dalje pa je urađen KT pregled endokranijuma – levo frontalno uočena je ekspanzivna formacija hipodenzne strukture, sa nepravilnim zonama nekroze, prečnika 61 × 56 × 40 mm. Bolesnik je premešten u Neurohirurišku kliniku i učinjena je operacija. Patohistološki, utvrđeno je da se radilo o *Astrocytoma gradus IV* (*glioblastoma multiforme*). Nakon sedmodnevnog perioda stabilnosti i početnog povlačenja piramidnog deficita zaostalog nakon operacije, razvila se azotemija i bolesnik je egzitirao desetog dana hospitalizacije u odeljenju neurohirurgije (slika 2).



**Sl. 2 – Nalaz kompjuterizovane tomografije (KT) kod trećeg bolesnika: levo frontalno ekspanzivna formacija hipodenzne strukture, sa nepravilnim zonama nekroze, prečnika 61 × 56 × 40 mm**

**Diskusija**

U radu su prikazana tri bolesnika koji su zbog primarno prisutne psihijatrijske fenomenologije upućeni psihijatru, a da je vrlo brzo tokom psihijatrijske hospitalizacije, kod njih utvrđeno postojanje tumora mozga. Veza tumora i psihopatologije može se sagledavati iz tri perspektive: bolesnici sa dijagnostikovanim tumorom mogu imati psihičke izmene, psihičke izmene mogu se pojaviti tokom napredovanja bolesti [18] ili, nedijagnostikovan tumor može imati samo psihičke manifestacije („neurološki nemi tumori"), što je utvrđeno i u našem radu.

Prema Međunarodnoj klasifikaciji bolesti – deseta revizija (MKB –10) [19], kod prikazanih bolesnika postavljene su sledeće dijagnoze: kod prve bolesnice je pre psihijatrijske hospitalizacije postavljena dijagnoza opsesivno-kompulzivnog poremećaja (F42); drugi bolesnik na prijemu označen je fenomenološki (paranoidno depresivno ispoljavanje) jer nije ispunjavao sve uslove ni za jedan psihijatrijski poremećaj; diferencijalno dijagnostički, bolesnik je mogao da bude shvaćen kao veliki depresivni poremećaj, sa psihotičnim simptomima (F32.3) ili kao perzistentni poremećaj sa sumanutošću, nespecifikovan (F22.9); kod trećeg bolesnika prethodno je postavljena dijagnoza alkoholizma (F10).

Kod sva tri bolesnika, pri prijemu nije bilo odstupanja u neurološkom nalazu. Kod prva dva bolesnika bile su prisutne glavobolje, ali je dominantna psihijatrijska simptomatologija prevagnula pri upućivanju bolesnika na inicijalno lečenje psihijatru. Ipak, glavobolja kod prve bolesnice i drugog bolesnika, kao i promena mentalnog statusa kod drugog bolesnika i trećeg bolesnika usmerila je komplementarna ispitivanja pa su urađeni: pregled očnog dna, elektronecefalografija, angiografija, KT i pregled endokranijuma. Ovim metodama dijagnostikovano je postojanje tumora mozga.

U slučajevima kao kod prve bolesnice i drugog bolesnika, jasna psihijatrijska simptomatologija, bez neuroloških poremećaja, opravdano je usmerila ove bolesnika prema psihijatru. Ipak, slučaj prve bolesnice nas upozorava da kod upornih opsesivnih simptoma, komplikovanih kompulzivnih rituala, kada izostaje terapijski efekat i nakon duže primene terapije, opravdano je češće ponavljati preglede i planirati dijagnostiku neurosnimanjem. Iako brojnim novim istraživanjima, uloga insule, multimodalnog moždanog lobusa, i dalje nije sasvim razjašnjena [20, 21], novija ispitivanja neurosnimanjem pokazuju da je insularni korteks uključen kod mnogih neuropsihijatrijskih poremećaja [22] – poremećaja raspoloženja, paničnog poremećaja, posttraumatskog stresnog poremećaja, opsesivno komuplzivnog poremećaja [21, 22], poremećaja ishrane i šizofrenije [22]. Ispitivanja cerebrovaskularnog protoka (rCBF) u insularnom korteksu kod bolesnika sa opsesivno-kompulzivnim poremećajem pokazuju da se intezivi-ranjem anksioznosti kod ovih bolesnika povećava protok u insularnom korteksu što donekle pomaže razumevanju uloge ove anatomske zone u OKP [22, 23].

Kod drugog bolesnika, starog 48 godina, dijagnostikovan je parijeto-temporalni astrocitom u desnoj hemisferi, a primarno je prezentovan depresivnošću udruženom sa paranoidnom simptomatologijom što je u skladu sa nalazom da je

inicijalne manifestacije primarnog moždanog tumora tokom pete decenije života često teško diferencirati od funkcionalnih psihijatrijskih poremećaja [18, 24]. Kompleksna prezentujuća klinička slika u formi paranoidno-depresivnog sindroma, u odsustvu neuroloških simptoma, ali sa razvojem promena u mentalnom statusu kao u slučaju drugog bolesnika, samo potvrđuje koliko različitih manifestacija može imati tumor mozga, kao i da se tumor mozga može otkriti kod bolesnika koji prvi put pokazuju psihijatrijske simptome ili je kod njih već postavljena psihijatrijska dijagnoza [17, 25].

Treći bolesnik upućen je psihijatru zbog dugogodišnjeg konzumiranja alkohola, iako je dva meseca pre prijema apstinirao. Od dana prijema ispoljavao je kliničke simptome organskog moždanog sindroma sa brzom progresijom koji se nisu mogli dovesti u vezu sa somatskim ili psihičkim manifestacijama alkoholizma – stanje na prijemu sa nesigurnom vremenskom orijentacijom, usporenim misaonim tokom, hipertenacitetnom pažnjom i intaktanim neurološkim nalazom preraslo je četvrtog dana hospitalizacije u dezorjentaciju u svim modalitetima, nemogućnost uspostavljanja verbalnog kontakta i izraženu psihomotornu usporenost uz gubitak kontrole sfinktera. Uopšte uzev, tumori mozga koji jako brzo progrediraju primarno se manifestuju organskim moždanim psihosindromima [2] dok se kod tumora mozga koji sporije progrediraju češće sreću promene ličnosti. U slučaju trećeg bolesnika, promene ličnosti koje bi se mogle pripisati tumoru frontalne regije nisu uočene jer se ove promene i, inače, ređe uočavaju kod bolesnika kod kojih se neki od ovih simptoma očekuju kao deo prethodno postavljene psihijatrijske dijagnoze [16].

Drugi i treći bolesnik potvrđuju ranija zapažanja [2, 6, 17, 18] o tome kako se lako psihijatrijski simptomi razumeju kao funkcionalni u svojoj etiologiji, što može imati za posledicu pogrešno ili zakasnelo postavljanje prave dijagnoze. Posebno bi trebalo naglasiti da se kao u slučaju trećeg bolesnika, podatak o prethodnom postojanju psihijatrijskog oboljenja (alkoholizam je jedan od čestih slučajeva), iako aktuelno psihijatrijske simptomatologije nema, zanemaruju somatske smetnje takvih bolesnika, a psihijatrijski bolesnik ostaje zarobljen ili etiketiran svojom prethodnom dijagnozom.

## Zaključak

Psihijatrijski poremećaji mogu biti primarna manifestacija moždanih tumora ili se tumori mozga mogu otkriti kod bolesnika kod kojih je već postavljena psihijatrijska dijagnoza. Ovi poremećaji nisu dovoljno specifični, mogu imati istovetnu kliničku prezentaciju kao i funkcionalni psihijatrijski poremećaji i tako mogu kompromitovati rano otkrivanje bolesti. Treba imati na umu „neurološki neme“ tumore mozga kao diferencijalno dijagnostičku mogućnost kod bolesnika sa netipičnom psihijatrijskom prezentacijom, kod terapijski-rezistentnih psihijatrijskih poremećaja, kao i kod bolesnika sa neočekivanim promenama u mentalnom statusu. Neuroimidžing dijagnostika, kao deo rutinskog dijagnostičkog postupka, u ovim situacijama, uz detaljnu anamnezu i ponavljane kliničke preglede, može umanjiti rizik od kasnog otkrivanja tumora.

## Zahvalnica

Ovaj rad je deo projekata br. 175014 i 175007 finansijski podržanih od strane Ministarstva za nauku i tehnološki razvoj Republike Srbije.

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Primljen 28. VI 2010.
Prihvaćen 2. VII 2010.

I N M E M O R I A M

# SVETLANA STAJIĆ (1957–2011)

Dana 21. 07. 2011. godine, nakon kratke i teške bolesti, preminula je Svetlana Ceca Stajić, dugogodišnji član Instituta za naučne informacije Vojnomedicinske akademije (VMA) u Beogradu i, gotovo punih 20 godina, stalni član Redakcije „Vojnosanitetskog pregleda“.

Osim poslova operatera zaduženog za pripremu časopisa za štampu, poslednjih 10 godina vršila je i dužnost sekretarice načelnika Instituta i oba posla obavljala je s takvom lakoćom i požrtvovanošću kakva se danas retko sreće. Ništa joj nije bilo teško i do poslednjeg trenutka nastojala je da nauči i savlada sve veštine kompjuterske i grafičke obrade teksta pomažući i ostalim članovima kolektiva da se obuče. Mnogi autori našeg časopisa, pogotovo oni iz VMA, pamtiće je po ljubaznosti i spremnosti da pomogne kad god je to bilo potrebno.

Slobodno se može reći da je Ceca bila oličenje svih vrlina na koje pomislimo kada za nekoga kažemo da je ČOVEK. Bila je razborita, odmerena, skromna, nenametljiva, marljiva, nesvakidašnje obzirna, istančanih manira, lepo vaspitana, u najboljem smislu te reči. Kao takva, bila je stub svoje porodice, koju je neizmerno volela i poštovala, i za koju joj nije bilo ništa teško učiniti. Ali ne samo za porodicu, već i za prijatelje, kolege, sve koji su joj se bilo kada obratili za pomoć. Čak i kada joj je bilo najteže, vodila je brigu o svima nama, nastojeći da smirenošću i vedrinom olakša teskobu i neizvesnost koju smo osećali suočeni sa njenom bolesti.

Zbog toga smo, njenim preranim odlaskom, izgubili svi. Pamtićemo je po dobroti, plemenitosti, velikom radnom elenu i, milom i toplom osmehu koji je svima nama iz Redakcije časopisa “Vojnosanitetski pregled” ulepšavao svaki dan.

Draga Ceco, počivaj u miru! Neka ti je večna slava i hvala!

**Redakcija „Vojnosanitetskog pregleda“**

# ERRATUM

*Igor B Jovanović, Miroslav Samardžić, Mirjana Nagulić, Vladimir Baščarević, Mirko Mićović, Svetlana Milošević*
**Primitivna trigeminalna arterija udružena sa arteriovenskom malformacijom cerebeluma**
Primitive trigeminal artery commorbid with aterovenous malformation of cerebellum

**Vojnosanit Pregl 2011; 68(8): 699–704.**

*Erratum in*: **Vojnosanit Pregl 2011; 68(9):**

*Igor B Jovanović, Miroslav Samardžić, Mirjana Nagulić, Vladimir Baščarević, Mirko Mićović, Svetlana Milošević*
**Primitivna trigeminalna arterija udružena sa arteriovenskom malformacijom cerebeluma**
Primitive trigeminal artery associated with arteriovenous malformation of cerebellum

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**Primeri oblika referenci**:

*Đurović BM*. Endothelial trauma in the surgery of cataract. Vojnosanit Pregl 2004; 61(5): 491–7. (Serbian)

*Balint B.* From the haemotherapy to the haemomodulation. Beograd: Zavod za udžbenike i nastavna sredstva; 2001. (Serbian)

*Mladenović T, Kandolf L, Mijušković ŽP.* Lasers in dermatology. In: *Karadaglić Đ*, editor. Dermatology. Beograd: Vojnoizdavački zavod & Verzal Press; 2000. p. 1437–49. (Serbian)

*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.

*Abood S.* Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

***Tabele***

Sve tabele štampaju se sa proredom 1,5 na posebnom listu hartije. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u desnom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, ne u zaglavlju. Za fus-notu koristiti sledeće simbole ovim redosledom: ***, †, ‡, §,** ||**, ¶, **, ††, ... .** Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

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Examples of references:

*Jurhar-Pavlova M, Petlichkovski A, TrajkovD, Efinska-Mladenovska O, Arsov T, Strezova A,* et al. Influence of the elevated ambient temperature on immunoglobulin G and immunoglobulin G subclasses in sera of Wistar rats. Vojnosanit Pregl 2003; 60(6): 657–612.

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Blinder MA. Anemia and Transfusion Therapy. In: Ahya NS, Flood K, Paranjothi S, editors. The Washington Manual of Medical Therapeutics, 30th edition. Boston: Lippincot, Williams and Wilkins; 2001. p. 413-28.

*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.

*Abood S.* Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

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Type each table double-spaced on a separate sheet. Number tables consecutively in the order of their first citation in the text in the upper right corner **(Table 1)** and supply a brief title for each. Place explanatory matter in footnotes, using the following symbols, in this sequence: ***, †, ‡, §, ||, ¶, **, ††, ... .** Each table has to be mentioned in the text. If you use data from another source, acknowledge fully.

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