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SADRŽAJ / CONTENTS

ORIGINALNI RADOVI / ORIGINAL ARTICLES

PREGLEDNI RAD / REVIEW ARTICLES

AKTUELNA TEMA / CURRENT TOPIC

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POREMEĆAJ SPAVANJA I FUNKCIONALNA ONESPOSOBLJENOST USLED HRONIČNOG BOLA U DONJEM DELU LEĐA

SLEEP DISORDER AND FUNCTIONAL DISABILITY IN CHRONIC LOW BACK PAIN

Jandrić -Kočić Marijana[1]

SAŽETAK

Uvod/Cilj: Hronični bol u donjem delu leđa često je praćen promenama u trajanju i kvalitetu sna. S druge strane, narušena struktura sna negativno utiče na kvalitet života obolelih. Cilj istraživanja je bio da se ispita da li postoji veza između prisustva poremećaja spavanja i stepena funkcionalne onesposobljenosti kod osoba sa hroničnim bolom u donjem delu leđa.
Metode: Studijom preseka obuhvaćeno je 150 osoba sa hroničnim bolom u donjem delu leđa koje su se javile u Dom zdravlja Krupa na Uni u periodu od 01.10.2016. do 01.10. 2018.godine. Pored opšteg upitnika, u istraživanju su korišćeni Upitnik o nesposobnosti po Rolandu Morisu (engl. *Roland Morris Disability Questionnaire*) i Pitsburčki indeks kvaliteta sna (engl. *Pittsburgh Sleep Quality Index*). U statističkoj analizi podataka primenjen je hi kvadrat test.
Rezultati: Od 150 osoba sa hroničnim bolom u donjem delu leđa 88 (58,7%) su činile žene, a 62 (41,3%) muškarci. Prosečna starost ispitanika je bila 54,0 ± 5,7 godina. Žene su bile statistički značajno starije nego muškarci. Muškarci i žene, kao i osobe uzrasta 40-59 godina i 60-79 godina, sa narušenim kvalitetom sna su značajno češće imali viši stepen funkcionalne onesposobljenosti nego osobe sa nenarušenim kvalitetom sna. Kod najmlađih osoba (20-39 godina) sa niskom funkcionalnom onesposobljenošću 5,3% je imalo narušen kvalitet sna, a 4,3% u uzrastu 40-59 godina i 4,0% u uzrastu 60-79 godina. Među osobama sa višim stepenom funkcionalne onesposobljenosti ni jedna osoba nije imala narušen kvalitet sna u uzrastu 20-39 godina, a sve osobe uzrasta 40-59 i 60-79 godina su imale narušen san.
Zaključak: Neophodna su dalja istraživanja o povezanosti kvaliteta sna i stepena funkcionalne onesposobljenosti osoba sa hroničnim bolom u donjem delu leđa. Edukacija o higijeni spavanja, rutinska procena kvaliteta sna i rana terapijska intervencija kod osoba sa hroničnim bolom u donjem delu leđa mogu doprineti smanjivanju funkcionalne onesposobljenosti, kao i troškova zdravstvene zaštite i radnog apsentizma.

SUMMARY

Introduction/Aim: Chronic lower back pain is often accompanied by changes in sleep duration and quality. On the other hand, disturbed sleep structure has a negative impact on the quality of life of patients. The aim of this study was to investigate whether there is relationship between the presence of sleep disorders and the degree of functional disability in patients with chronic low back pain.
Methods: A cross-sectional study included 150 people with chronic lower back pain who were admitted at the Krupa Health Center at Uni in the period 01 10.2016. to 01.10 2018. In addition to general questionnaire, the survey used Roland Morris Disability Questionnaire and the Pittsburgh Sleep Quality Index. The chi-square test was used in the statistical analysis of the dana.
Results: Of the 150 people with chronic low back pain, 88 (58.7%) were women and 62 (41.3%) were men. The average age of the subjects was 54.0 ± 5.7 years. Women were statistically significantly older than men. Men and women, as well as people aged 40-59 and 60-79 years, with impaired quality of sleep were significantly more likely to have a higher degree of functional disability than persons with undermined quality of sleep. In the youngest group (20-39 years),of persons with low functional disability 5.3% of them had poor sleep quality, 4.3% in group aged 40-59 years and 4.0% aged 60-79 years. Among persons with higher levels of functional disability, none had impaired sleep quality at the age of 20-39 years, and all persons aged 40-59 years and 60-79 years had impaired sleep quality.
Conclusion: Further research is needed on the relationship between the degree of functional disability of people with chronic low back pain and sleep quality. Sleep hygiene education, routine assessment of sleep quality, and early therapeutic intervention for disorders present in people with chronic low back pain can contribute to reducing functional disability as well as the cost of health care and occupational absenteeism.

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Ključne reči: spavanje, funkcionalna onesposobljenost, bol u donjem delu leđa

Keywords: sleep, functional disability, low back pain

Uvod

Na osnovu brojnih do sada sprovedenih istraživanja procenjuje se da čak 80% odraslih osoba ima bol u donjem delu leđa bar jednom u toku života (1-3). Nešto više zaposlenih muškaraca (5-7%) nego žena (4-6%) traži pomoć zbog bola u donjem delu leđa kod svog izabranog lekara primarne zdravstvene zaštite (1,2). Najčešće bol u donjem delu leđa pogađa radno aktivno stanovništvo (1,2). U većini zemalja sveta ukazuje se na velike troškove lečenja ovog stanja, a u Sjedinjenim Američkim Državama troškovi lečenja bola u donjem delu leđa su odmah iza troškova lečenja malignih i kardiovaskularnih bolesti (3). Posledice bola u donjem delu leđa mogu dovesti do niskog (smanjena radna produktivnost ali bez narušenih svakodnevnih rutinskih aktivnosti) ili visokog stepena funkcionalne onesposobljenosti (ograničene svakodnevne rutinske aktivnosti i to npr. umivanje, ustajanje iz stolice, okretanje u krevetu, oblačenje, obuvanje) (3). Hronični lumbalni bol često je praćen promenama u trajanju i kvalitetu sna (4,5). S druge strane, narušena struktura sna negativno utiče na kvalitet života obolelih (4,5).

Istraživanje je imalo za cilj da ispita da li postoji veza izmedju poremećaja spavanja i stepena funkcionalne onesposobljenosti kod osoba sa hroničnim bolom u donjem dijelu leđa.

Metode

Studijom preseka bilo je obuhvaćeno 150 osoba sa hroničnim bolom u donjem delu leđa koji su se u periodu od 24 meseca, od 01.10.2016. do 01.10.2018. godine, javili izabranom lekaru u Domu zdravlja Krupa na Uni (Bosna i Hercegovina). Kriterijumi za uključivanje ispitanika u istraživanje su bili: uzrast između 20 i 79 godina, završena osnovna škola i prisustvo hroničnog bola u donjem delu leđa u trajanju od najmanje tri meseca. Hronični bol u donjem delu leđa definiše se kao bol, mišićna napetost i nelagoda lokalizovana u području između donjeg rebarnog luka i donje glutealne brazde, sa širenjem u jednu, ređe obe noge, ili bez njega, koja traje duže od 120 dana (6). Iz studije su isključene osobe: starosti iznad 79 i ispod 20 godina, sa bolom u donjem dijelu leđa koji je trajao kraće od 120 dana, kao i sve osobe sa psihijatrijskim poremećajima, malignim i uznapredovalim hroničnim oboljenjima (hronična bubrežna insuficijencija, dekompenzacija srca, insuficijencija jetre), zapaljenskim reumatskim bolestima (ankilozirajući spondilitis i reumatoidni artritis), infekcijama (vertebralni osteomijelitis, tuberkulozni spondilitis) i akutnim traumama i operativnim zahvatima na lumbalnom delu kičmenog stuba.

Podaci su prikupljeni opštim i specifičnim upitnicima. Opštim upitnikom prikupljeni su demografski podaci (pol i uzrast).

Upitnik o nesposobnosti po Rolandu Morisu (engl. *Roland Morris Disability Questionnaire* - *RMDQ*) sastoji se od 24 pitanja pomoću kojih se procenjuje stepen funkcionalne onespososobljenosti kroz sledećih šest oblasti: fizička aktivnost, spavanje/odmor, psihosocijalno funkcionisanje, ishrana, kućni poslovi i učestalost bolova. Na osnovu ukupnog skora koji je niži od 15 smatra se da osobe imaju nizak stepen funkcionalne nesposobnosti, a sa skorom jednakim ili većim od 15 da su sa visokim stepenom funkcionalne nesposobnosti.

Pitsburški indeks kvaliteta sna (engl. *Pittsburgh Sleep Quality Index* - *PSQI*) je upitnik sačinjen od 19 pitanja, pomoću kojih se procenjuje kvalitet sna u poslednjih mesec dana kroz sedam oblasti: subjektivni kvalitet sna, latencija sna, trajanje sna, uobičajena efikasnost sna, poremećaj sna, korišćenje lekova za spavanje i dnevna disfunkcionalnost uzokovana narušenim kvalitetom sna (8,9). Svako pitanje se, u zavisnosti od odgovora, ocenjuje na skali od 1 do 3 i ukupan zbir daje PSQI skor. PSQI skor veći od 5 označava narušen kvalitetet sna. PSQI svojom pouzdanošću, merodavnošću, kratkoćom i dostupnošću prestavlja veliki potencijal za kliničku praksu (8,9).

U statističkoj analizi podataka primenjen je hi-kvadrat test.

Rezultati

Istraživanje je obuhvatilo 150 pacijenata. Među njima je bilo 88 (58,7%) žena i 62 (41,3%) muškaraca (Tabela 1). Najveći broj ispitanika sa hroničnim bolom u donjem delu leđa (58,7%) su bili životne dobi 40-59 godina. Prosečna starost ispitivane populacije bila je

54,0 ± 5,7 godina. Žene su bile statistički značajno starije nego muškarci.

Tabela 1. Distribucija osoba sa hroničnim bolom u donjem delu leđa prema polu i uzrastu / *Table 1. Distribution of people with chronic low back pain by gender and age*

Uzrast (godine)/ *Age (years)*	Muškarci/*Men* Broj (%)/*No (%)*	Žene/*Women* Broj (%)/*No (%)*	Ukupno/*Total* Broj (%)/*No (%)*
20-39	12 (8.0)	8 (5.3)	20 (13.3)
40-59	30 (20.0)	58 (38.7)	88 (58.7)
60-79	20 (13.3)	22 (14.7)	42 (28.0)
Ukupno/*Total*	62 (41.3)	88 (58.1)	150 (100.0)

p vrednost prema hi kvadrat testu<0.05 / *p value according to hi square test<0.05*

Osobe sa narušenim kvalitetom sna (skor veći od 5) su značajno češće imale viši stepen funkcionalne onesposobljenosti prema RMDQ upitniku (78,3%) nego osobe sa nenarušenim kvalitetom sna (0,0%) (Tabela 2). Identična situacija zabeležena je i kod muškaraca i žena kada su se oni posmatrali pojedinačno. Osobe uzrasta 40-59 godina i 60-79 godina sa narušenim kvalitetom sna su značajno češće imale viši stepen funkcionalne onesposobljenosti nego osobe sa nenarušenim kvalitetom sna. Kod osoba sa niskom funkcionalnom onesposobljenošću, 5,3% je imalo narušen kvalitet sna u uzrastu 20-39 godina, 4,3% u uzrastu 40-59 godina i 4,0% u uzrastu 60-79 godina. Među osobama sa višim stepenom funkcionalne onesposobljenosti ni jedna osoba nije imala narušen kvalitet sna u uzrastu 20-39 godina, a sve osobe uzrasta 40-59 i 60-79 godina.

Tabela 2. Distribucija osoba sa hroničnim bolom u donjem delu leđa sa narušenim i nenarušenim snom prema stepenu funkcionalne onesposobljenosti, polu i uzrastu / *Table 2. Distribution of persons with chronic low back pain with disturbed and undisturbed sleep acording to functional disability, gender and age*

Karakteristike/ *Characteristics*	Narušen kvalitet sna/ *Disturbed quality of sleep* PSQI>5 Broj (%/)/*No (%)*	Nenarušen kvalitet sna/ *Undisturbed quality of sleep* PSQI≤5 Broj (%)/*No (%)*	p vrednost*/ *p value**
Svi/*All*			
RMDQ<15**	15 (21.7)	81 (100.0)	
RMDQ≥15***	54 (78.3)	0 (0.0)	< 0.05
Muškarci/ *Men*			
RMDQ<15**	6 (25.0)	38 (100.0)	
RMDQ≥15***	18 (75.0)	0 (0.0)	< 0.05
Žene/ *Women*			
RMDQ<15**	9 (20.0)	43 (100.0)	
RMDQ≥15***	36 (80.0)	0 (0.0)	< 0.05
Uzrast 20-39 godina/ *20-39 years of age*			
RMDQ<15**	1 (100.0)	19 (100.0)	
RMDQ≥15***	0 (0.0)	0 (0.0)	-
Uzrast 40-49 godina/ *40-49 years of age*			
RMDQ<15**	2 (4.6)	44 (100.0)	
RMDQ≥15***	42 (95.4)	0 (0.0)	< 0.05
Uzrast 60-79 godina/ *60-79 years of age*			

*p prema hi kvadrat testu ili Fisher-ovom testu / **p value according to hi square test or Fisher test;* **Niži stepen funkcionalne onesposobljenosti / ***Lower degree of functional disability;* ***Viši stepen funkcionalne onesposobljenosti / **** Higher degree of functional disability;* PSQI - Pitsburški indeks kvaliteta sna / *Pittsburgh Sleep Quality Index;* RMDQ - Upitnik o nesposobnosti po Rolandu Morisu / *Roland Morris Disability Questionnaire.*

Diskusija

Poremećaji spavanja su čest i neretko neprepoznat komorbitet hroničnog bola u donjem delu leđa. U našoj studiji, narušen kvalitet sna je bio verifikovan od strane 69 (46,0%) osoba sa hroničnim bolom u donjem delu leđa. Studije sprovedene u Velikoj Britaniji došle su do sličnih rezultata (10), dok je u istraživanju grupe autora iz Poljske i Maroka taj procenat bio značajno viši, preko 80% (11). Prevalencija poremećaja spavanja u opštoj populaciji prema dijagnostičkom priručniku za mentalne bolesti iznosi 6% (11).

Rezultati našeg istraživanja ukazuju da su osobe sa narušenim kvalitetom sna statistički značajno češće imaju veći stepen funkcionalne onesposobljenosti i da je ona specifična za starije osobe (uzrasta 40-59 i 60-69 godina). Neke studije ukazuju na značajnu ulogu poremećaja spavanja u razvoju i održavanju funkcionalne onesposobljenosti (12,13). Sedamnaestogodišnja populaciona studija u Norveškoj utvrdila je da narušena struktura sna u akutnoj i subakutnoj fazi lumbalnog bola predstavlja značajan faktor

u nastanku hroničnog bola i povećanju stepena funkcionalne onesposobljenosti (14). Prospektivna dvadeset osmogodišnja studija u Finskoj dokazala je da pacijenti sa poremećajima spavanja imaju 2,4 puta veću verovatnoću za hospitalizaciju zbog hroničnog lumbalnog bola u odnosu na pacijente sa normalnom strukturom sna (13).

Nedostatak sna ili smanjeni kvalitet istog, smanjuje bolni prag i povećava funkcionalnu onesposobljenost kroz neurobiološku modifikaciju (smanjenu osetljivost mi i delta opoidnih receptora, smanjen bazalni nivo endogenih opoida) (14,15). Studija sa narušenim kontinuitetom sna (sedam buđenja u trajanju od 20 minuta i jedno buđenje u intervalu od 60 minuta) govori u prilogu poremećaja u silaznom modulacionom sistemu bola (smanjena endogena opoidna inhibicija), bez promena u uzlaznim senzornim putevima (14).

Promena dopaminergičke signalizacije navodi se kao mogući uzrok povezanosti kvaliteta sna, intenziteta bola i funkcionalne onesposobljenosti. Kod osoba sa hroničnim lumbalnim bolom i narušenom arhitekturom sna se verifikuje smanjeno oslobađanje dopamina i niža aktivacija D2/D3 receptora u ventralnom strijatumu (14,15). Nedostatak sna smanjuje promet 5-hidroksitriptamina (eng. 5-hidroxytryptamin, 5-HT), menja aktivnost serotoninskih neurona u rafe jedrima (engl. raphe nuclei) i utiče na 5-HT receptorske funkcije (14,15). Poremećaji spavanja kod odraslih osoba sa hroničnim bolom u donjem delu leđa rezultuju povećanjem proinflamatornih citokina, uključujući interleukin 6 (16). Medijatori upale moduliraju nociocepciju, doprinose pojačanju i upornosti bola i povećavaju funkcionalnu onesposobljenost (16).

Povećanje funkcionalne onesposobljenosti kod osoba sa hroničnim lumbalnim bolom se vezuje za pojavu alfa talasa u NREM (bez brzih pokreta očiju; eng. Non rapid eye movement, NREM) fazi sna (15). Eksperimenti na životinjama ukazuju da poremećaj REM (brzi pokreti očiju; eng. Rapid eye movement, REM) faze sna otežava sposobnost serotoninskog sistema da podrži analgeziju proizvedenu aktivnošću opoidergičkog sistema (15). Postoje indicije da poremećena struktura sna dovodi do promena u noradrenergičkom i holinergičkom neurotransmiterskom sistemu uključenih u modulaciju bola (15). Poremećaj spavanja rezultira dnevnom pospanošću, povećanjem umora, kognitivnom disfunkcijom i negativnim emocijama, što može izazvati ili oponašati hiperalgeziju i povećati funkcionalnu onesposobljenost (13).

Mnogi lekovi koji se koriste u kontroli bola narušavaju kvalitet sna čime se smanjuje njihov analgetski učinak i povećava funkcionalna onesposobljenost (17). Nesteroidni antinflamatorni lekovi smanjuju sintezu prostaglandina, suprimiraju oslobađanje melatonina i utiču na termogenezu (17). Antidepresivi (triciklični antidepresivi i selektivni inhibitori ponovnog preuzimanja serotonina) skraćuju trajanje REM faze sna, povećavaju dnevnu pospanost (17). Narušena struktura sna i povećanje dnevne somnolencije mogu indukovati opoidno indukovanu hiperalgeziju (17,18,19).

Iako nisu široko rasprostranjene, terapijske intervencije koje unapeđuju kvalitet sna kod osoba sa hroničnim lumbalnim bolom smanjuju bol i funkcionalnu onesposobljenost (12) . Shodno tome, evaluacija kvaliteta sna treba da bude deo inicijalne dijagnostičke obrade pacijenata sa hroničnim bolom u donjem delu leđa (12).

Ukoliko se kritički osvrnemo možemo konstatovati da u studiji preseka nije moguće odgovoriti na pitanje šta je uzrok a šta posledica, odnosno da li su ispitivane osobe sa hroničnim bolom u donjem delu leđa imale lošiju funkcionalnu onesposobljenost zbog narušenosti kvaliteta sna ili su zbog lošijeg kvaliteta sna razvile veći stepen funkcionalne onesposobljenosti. Osim toga, nije bilo moguće ispitati uticaj, pored kvaliteta sna, i drugih faktora koji mogu samostalno ili udruženo voditi lošijoj funkcionalnoj onesposobljenosti.

Zaključak

Neophodna su dalja istraživanja o vezi između kvaliteta sna i funkcionalne onesposobljenosti kod osoba sa bolom u donjem delu leđa. Poseban akcenat treba staviti na ispitivanje ove veze kod starijih osoba i identifikovati sve druge potencijalne faktore funkcionalne onesposobljenosti, a ne samo sna. Edukacija o higijeni spavanja, rutinska procena kvaliteta sna i rana terapijska intervencija prisutnih poremećaja kod osoba sa hroničnim bolom u donjem delu leđa mogu doprineti smanjivanju funkcionalne onesposobljenosti, kao i troškova zdravstvene zaštite i radnog apsentizma.

Literatura

1. Mačak - Hadžiomerović, A Čustović - Hadžimuratović A, Mujezinović A. Vodič za prevenciju i tretman lumbalnog bolnog sindroma. Sarajevo: Ministarstvo zdravstva Kantona Sarajevo, 2009. Available at: https://mz.ks.gov.ba/sites/mz.ks.gov.ba/files/Lumbalni%20bolni%20sindrom2.pdf.
2. Stanković A. Primena individualno koncipiranog kineziterapijskog tretmana i kognitivno-bihejvioralne terapije u lečenju hroničnog bolnog lumbalnog sindroma. Doktorska disertacija. Niš: Medicinski fakultet Univerziteta u Nišu, 2015. Available at: https:// file:///C:/Users/marijanajandrickocic/Downloads/Dis_UNI_Anita_M_Stankovic_2015.pdf.
3. Jandrić-Kočić M. Comorbidities and functional disability in chronic low back pain. Opšta medicina 2019; 25(3-4): 43-57.
4. Purushothaman B, Singh A, Lingutla K, Bhatia Ch , Pollock R, Krishna M. Prevalence of insomnia in patients with chronic back pain. J Orthop Surg 2013;21(1):68-70.
5. Sousa Vanessa Patrícia Soares de, Ribeiro Silvia Oliveira, Aquino Carla Monique Ribeiro de, Viana Elizabel de Souza Ramalho. Quality of sleep in pregnant woman with low back pain. Fisioter Mov 2015; 28(2): 319-326. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0103-51502015000200319&lng=en.
6. Vrbanić TS. Low back pain – from definition to diagnosis. Reumatizam 2011;5 8(2):105-7.
7. Stevens M, Lin C, Maher C. The Roland Morris Disability Questionnare. J Psysioter 2016; 62(2): 1165.
8. Beaudreau SA, Spira AP, Stewart A, Kezirian EJ, Lui LY, Ensrud K,et al. Validation of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale in older black and white women. Sleep Med 2012; 13(1):36–42.
9. Buysse DJ, Hall ML, Strollo PJ, Kamarck TW, Owens J, Lee L, Reis SE, Matthews KA. Relationships between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and clinical/polysomnographic measures in a community sample. J Clin Sleep Med 2008; 4(6):563-71.
10. Marty M, Rozenberg S, Duplan B, Thomas P, Duquesnoy B, Allaert F, Section Rachis de la Société Française de Rhumatologie. Quality of sleep in patients with chronic low back pain: a case-control study. Eur Spine J 2008; 17(6):839–844.
11. Uchmanowicz I, Kołtuniuk A, Stepien A, Uchmanowicz B. The influence of sleep disorders on the quality of life in patients with chronic low back pain. Scand J Caring Sci 2019; 33:119–127.
12. Siengsukon C, Nirmala Margaret Emmanuel RN, Sharma NK. Relationship between low back pain and sleep quality. J Nov Physiother 2013;3:168.
13. Alsaadi SM, McAuley JH, Hush JM, Maher CG. Prevalence of sleep disturbance in patients with low back pain. Eur Spine J 2011; 20(5):737–743.
14. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain 2013;14(12):1539–1552.
15. Kundermann B, Krieg JC, Schreiber W, Lautenbacher S. The Effects of Sleep Deprivation on Pain. Pain ResManag 2004; 9(1):25-32.
16. Heffner KL, France CR, Trost Z, Ng HM, Pigeon WR. Chronic low back pain, sleep disturbance, and interleukin-6. Clin J Pain 2011; 27(1):35–41.
17. Bohra MH, Kaushik C, Temple D, Chung SA, Shapiro CM. Weighing the balance: how analgesics used in chronic pain influence sleep? Br J Pain 2014; 8(3):107–118.
18. Murase K, Tabara Y, Ito H, Kobayashi M, Takahashi Y, Setoh K, et al. Knee Pain and Low Back Pain Additively Disturb Sleep in the General Population: A Cross-Sectional Analysis of the Nagahama Study. PLoS One 2015; 10(10):e0140058.
19. Robertson JA, Purple RJ, Cole P, Zaiwalla Z, Wulff K, Pattinson KT. Sleep disturbance in patients taking opioid medication for chronic back pain. Anaesthesia 2016; 71(11):1296–1307.

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VISOKA PREVALENCIJA DIJABETESNE KETOACIDOZE KOD MLADIH SA NOVOOTKRIVENIM TIPOM 1 DJABETESA MELITUSA U BEOGRADU: DESETOGODIŠNJE ISKUSTVO TERCIJERNOG CENTRA

HIGH PREVALENCE OF DIABETIC KETOACIDOSIS IN CHILDREN WITH NEWLY DIAGNOSED TYPE 1 DIABETES IN BELGRADE, SERBIA: 10-YEAR TERTIARY CENTRE EXPERIENCE

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SAŽETAK

Uvod/cilj: Dijabetesna ketoacidoza (DKA) je najznačajniji uzrok mortaliteta mladih sa tipom 1 dijabetesa melitusa (T1DM). Rezultati poslednjih istraživanja ukazuju na zabrinjavajuće visoku prevalenciju DKA u trenutku postavljanja dijagnoze T1DM kod mladih u Beogradu. Cilj ovog istraživanja bila je procena učestalosti DKA kod dece i adolescenata sa novootkrivenim T1DM tokom desetogodišnjeg perioda u tercijernom centru u Beogradu.
Metode: Podaci su prikupljeni retrospektivnom pretragom medicinske dokumentacije sve dece i adolescenata sa novootkrivenim T1DM koji su bili hospitalizovani u našem centru tokom perioda od 1. januara 2007. godine do 1. januara 2017. godine.
Rezultati: Dijagnoza novootkrivenog T1DM postavljena je kod ukupno 501 deteta (233 devojčice i 268 dečaka) prosečnog uzrasta 9,55 ± 4,26 godina, sa prosečnom vrednošću pH od 7,28 ± 0,14 (6,78-7,51) u trenutku postavljanja dijagnoze. Devojčice sa T1DM su u proseku bile mlađe u odnosu na dečake (9,05 ± 4,04 god. u odnosu na 9,98 ± 4,41 god, respektivno, p<0.05). Od ukupnog broja pacijenata, 191 (38,1%) je u trenutku postavljanja dijagnoze imao DKA, od čega je 47.6% bilo u blagoj, 26,2% u umerenoj, a 26,2% u teškoj ketoacidozi. U grupi mlađe dece, uočena je veća učestalost DKA (40%) u odnosu na grupu dece uzrasta > 11 godina (35%), ali ova razlika nije bila statistički značajna.
Zaključak: Rezultati ukazuju na zabrinjavajuće visoku prevalenciju DKA u trenutku postavljanja dijagnoze T1DM kod mladih u Beogradu, bez značajne razlike u odnosu na uzrast. Ovi nalazi ukazuju na potrebu

SUMMARY

Introduction/Aim: Diabetic ketoacidosis (DKA) is one of the most important causes of acute mortality in youth with type 1 diabetes mellitus (T1DM). Recently published data suggested worryingly high frequency of DKA at the onset of T1DM in Belgrade youth. The goal of this study was to assess the frequency of DKA at the onset of T1DM and the associated risk factors in Belgrade youth during the previous 10 years at a tertiary centre.
Methods: Data were collected retrospectively from the medical records of all children with new-onset T1DM admitted to our centre during the study period between 1st January 2007 and 1st January 2017.
Results: During the study period, a total of 501 subjects (233 girls and 268 boys) were diagnosed with new-onset T1DM, with a mean age of 9.55 ± 4.26 years, and mean pH at the time of diagnosis of 7.28 ± 0.14 (6.78-7.51). Girls with T1DM were younger compared to boys (9.05 ± 4.04 years vs. 9.98 ± 4.41 years, respectively, p < 0.05). Of all patients, 191 (38.1%) presented with DKA, 47.6% of which were classified as mild, 26.2% as moderate and 26.2% as severe DKA. Slightly higher frequency of DKA was noticed in the younger age groups (40%) compared to the children > 11 years (35%), although this difference was not statistically significant.
Conclusion: There is an alarmingly high rate of DKA at the onset of T1DM in Belgrade youth with no significant differences between different age groups. These findings emphasize the need for intensive public health preventive actions aimed at early diagnosis of T1DM in all age groups.

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za intenzivnim javno-zdravstvenim merama prevencije ketoacidoze, odnosno pravovremenog postavljanja dijagnoze T1DM kod dece i adolescenata u Beogradu.
Ključne reči: Dijabetesna ketoacidoza, dijabetes melitus tipa 1, deca, prevencija, epidemiologija

Keywords: Diabetic ketoacidosis, type 1 diabetes mellitus, children, prevention, epidemiology

Introduction

Diabetic ketoacidosis (DKA) is one of the most important causes of acute mortality in youth with type 1 diabetes mellitus (T1DM) (1,2). The frequency of DKA at the time of diagnosis of T1DM is highly variable, with worldwide reported incidences ranging from 12.8 to 80% (3-18).

Serbia has a population of children under the age of 19 years of 1,427,272, and a large proportion of youth (317,258 - 22%) lives in Belgrade, the capital city (19). There are two tertiary paediatric centres in Belgrade with paediatric endocrinology departments and intensive care units in which the children with newly diagnosed T1DM are treated: the University Children's Hospital, and our hospital the Mother and Child Healthcare Institute of Serbia "Dr Vukan Cupic" (18). Besides those residing in Belgrade, children from other parts of Serbia are also frequently being referred to these two centres in Belgrade at the time of diagnosis due to the lack of resources in other regions.

The recently published data from the University Children's Hospital in Belgrade, the other tertiary centre from Belgrade, revealed alarmingly high frequency of DKA (32.9%) in youth with newly diagnosed T1DM during the period 1991-2011, with DKA frequency up to 55% in children younger than 5 years (18). Considering that such high prevalence of DKA in children and adolescents with newly diagnosed T1DM represents a worrisome and significant public-health issue, we analyzed the medical records of patients diagnosed at our centre in order to provide a comprehensive insight into the frequency of DKA in youth with newly diagnosed T1DM living in the Belgrade area.

The aim of the present study was to analyze the frequency of DKA and the associated risk factors at the time of onset of T1DM during the period of the past 10 years (2007-2017) at our hospital, the other tertiary centre in Belgrade, Serbia.

Methods

The data were collected retrospectively from the medical records of all children with new-onset T1DM admitted to the Mother and Child Healthcare Institute of Serbia "Dr Vukan Cupic" during the study period between 1st January 2007 and 1st January 2017. Subjects with other types of diabetes were excluded from this study. Data regarding patients' gender, age at diagnosis, duration of symptoms, blood pH (or serum bicarbonates when pH was unavailable), glucose and blood glycosylated haemoglobin (HbA1c) level at the time of diagnosis were collected retrospectively from the medical records. Study protocol was approved by the Hospital Ethics Committee and was in accordance with the Declaration of Helsinki.

The final study cohort included 501 patients (233 girls and 268 boys) with newly diagnosed T1DM. The patients were classified into three age groups: under 5 years, 5-11 years and > 11 years. Based on the date of admission, the study period was also stratified into two 5-year periods.

The diagnosis of DKA was based on ISPAD 2014 guidelines: hyperglycaemia (blood glucose > 11 mmol/L) with acidosis (venous pH < 7.3 or bicarbonate < 15 mmol/L), and with ketonaemia or ketonuria (20). DKA severity was also categorized according to the ISPAD 2014 guidelines as mild (venous pH < 7.3, bicarbonate < 15 mmol/L), moderate (pH < 7.2, bicarbonate < 10 mmol/L) or severe (pH < 7.1, bicarbonate < 5 mmol/L) (20).

Differences in the means between groups were tested using the independent t-test, Mann-Whitney U test and Kruskal-Wallis independent samples test, depending on the number of groups and the distribution of the variables, and the Pearson's chi-square test was used for categorical variables. P-values < 0.05 were considered as statistically significant. Analyses were conducted using the SPSS version 20 (SPSS Inc, Chicago, IL) statistical software.

Results

Of all 501 patients with T1DM, 191 (38.1%) presented with DKA and 310 (61.9%) without DKA (Table 1). DKA was present at the time of diagnosis slightly more often in newly diagnosed girls (40.8%) compared to boys (35.8%); however, the difference was not statistically significant. In the group of patients without DKA, the mean age was 9.73 ± 4.26 years which was a slightly higher than in the group with DKA 9.25 ± 4.27. In the group of patients with DKA, mean blood glucose level was significantly higher than in the group without DKA. As expected, the mean pH among patients with DKA was significantly lower. Also, the level of HbA1c was significantly higher in the group with DKA than in the group without DKA. Patients with DKA had a slightly shorter duration of symptoms, but without statistically significant difference.

Table 1. Characteristics of patients with or without diabetic ketoacidosis*

	No DKA (Mean±SD)	Ranges	DKA (Mean±SD)	Ranges	p value*
N	310		191		
Age at diagnosis (years)	9.73 ± 4.26	1.24 -17.72	9.25 ± 4.27	0.93-18.74	NS
Sex ratio (males %)	55.5%		50.3%		NS**
Biochemical parameters					
pH	7.37 ± 0.04	7.30 -7.51	7.15 ± 0.12	6.78-7.29	<0.001
Glucose (mmol/L)	21.8 ± 8.6	7.3-55.0	25.5 ± 8.4	10.1-57.8	<0.001
HbA1c (%)	11.4 ± 2.2	6.3-18.9	12.2 ± 2.1	7.6-19.7	0.001
Duration of symptoms (days)	20.7 ± 21.1	0-155	21.3 ± 21.2	0-120	NS

No DKA – patients without diabetic ketoacidosis at the time of T1DM diagnosis; DKA – patients with diabetic ketoacidosis at the time of T1DM diagnosis; NS – not statistically significant; *p value according to the t test; **p value according to Pearson's chi-square test.

When subjects were compared according to DKA severity at the onset of T1DM, there were no significant differences in age at diagnosis, gender, or levels of HbA1c (Table 2). As expected, pH level ($p < 0.001$) was significantly lower in the groups with moderate and severe DKA, and interestingly, blood glucose levels were significantly higher in the group with severe DKA ($p = 0.002$).

Table 2. Characteristics of patients with diabetic ketoacidosis (DKA) (N = 310) at time of diagnosis regarding DKA severity

	Mild DKA	Moderate DKA	Severe DKA	p value*
N (proportion of cohort)	91 (47.8%)	50 (26.2%)	50 (26.2%)	
Age at diagnosis (years)	10.0 ± 4.4	8.5 ± 3.5	8.6 ± 4.6	NS
Sex ratio (males %)	51%	50%	50%	NS**
Biochemical parameters				
pH	7.25 ± 0.03	7.16 ± 0.03	6.98 ± 0.07	< 0.001
Glucose (mmol/L)	23.9 ± 8.3	24.4 ± 5.8	29.4 ± 9.6	0.002
HbA1c (%)	12.4 ± 2.1	12.3 ± 2.1	11.9 ± 2.3	NS

NS – not statistically significant; *p value according to the Kruskal-Wallis independent samples test; **p value according to Pearson's chi-square test

There were 96 children (19.2%) aged less than 5 years at the time of diagnosis of T1DM (Table 3). The incidence of DKA in this age group was 40.6% (n = 39), without statistically significant differences in DKA prevalence in older age groups, as shown in Table 3. In the youngest age group, higher frequency of severe DKA was observed, but also, without any statistical significance. Slightly higher levels of HbA1c were observed in older age groups. There was no significant difference in the duration of symptoms among different age groups.

Table 3. Characteristics of patients with newly diagnosed T1DM in different age groups

Characteristics	< 5 years (N=96)	5-11 years (N=198)	>11 years (N=207)	p value*
DKA at diagnosis, n (%)	39 (40.6%)	80 (40.4%)	72 (34.8%)	NS**
Severity of DKA				
Mild	16 (41.05%)	33 (41.3%)	42 (58.3%)	NS**
Moderate	10 (25.6%)	28 (35.0%)	12 (16.7%)	NS**
Severe	13 (33.3%)	19 (23.8%)	18 (25.0%)	NS**
Laboratory findings				
Blood glucose level (mmol/L)	22.5±8.6 (8.8-55.0)	22.9±7.8 (8.0-53.0)	23.8±9.5 (7.3-57.8)	NS
pH	7.27±0.16 (6.88-7.50)	7.27±0.13 (6.91 - 7.51)	7.28±0.13 (6.78 - 7.48)	NS
HbA1c (%)	10.7±1.9 (6.4-16.1)	11.7±2.2 (6.3-19.7)	12.2±2.2 (6.6-18.9)	< 0.001
Duration of symptoms (days)	16.8±17.7 (2-120)	21.7±22.9 (0-155)	22.1±20.6 (0-120)	NS

DKA –diabetic ketoacidosis; NS – not statistically significant; *p value according to the t test; NS – not statistically significant; *p value according to the Kruskal-Wallis independent samples test; **p value according to Pearson's chi-square test.

We also compared the first half of the study period with the last 5-year period (Table 4). In 2007-2011 period, the incidence of DKA at the time of diagnosis of T1DM, as well as the percentage of severe DKA were slightly higher, but without statistically significant difference, as shown in Table 4. Also, there were no significant differences between periods regarding the age at diagnosis of T1DM, blood glucose levels, pH or HbA1c levels.

Table 4. Comparison of children diagnosed with type 1 diabetes between 2007-2011 and 2012-2016.

Characteristics	2007-2011 (N=267)	2012-2016 (N=234)	p value
Age at diagnosis (years)	9.3±4.4 (0.9-18.7)	9.8±4.1 (1.4-18.0)	NS
Blood glucose (mmol/L)	22.9±9.0 (7.3-57.8)	23.4±8.3 (8.0-49.6)	NS
pH	7.26±0.14 (6.90-7.49)	7.29±0.13 (6.78-7.51)	NS
HbA1c (%)	11.5±2.3 (6.6-19.7)	11.9 ±2.1 (6.3-17.5)	NS
DKA n (%)	108 (40.4%)	83 (35.5%)	NS
Mild	52 (48.1%)	39 (47.0%)	NS**
Moderate	22 (20.4%)	28 (33.7%)	NS**
Severe	34 (31.5%)	16 (19.3%)	NS**

* DKA –diabetic ketoacidosis; NS – not statistically significant; p value according to t-test; *p value according to the t test; **p value according to Pearson's chi-square test.

Discussion

Mother and Child Healthcare Institute of Serbia "Dr Vukan Cupic" is the largest paediatric hospital in Serbia and one of the two tertiary centres in the capital city Belgrade that treats children with T1DM from the Belgrade area. Considering the high prevalence of DKA at the time of T1DM diagnosis recently reported by the authors from the other tertiary centre from Belgrade, and that such a high prevalence of DKA represents a worrisome public-health issue, this study analyzed the data from medical records of patients diagnosed at our centre, to provide a complete insight into the DKA at the onset of T1DM in children and adolescents living in Belgrade (18).

The frequency of DKA at the time of diagnosis of T1DM is known to be highly variable (3-17). In our study, 38.1% newly

diagnosed T1DM patients had DKA, which, together with the DKA incidence of 32.9% reported by the study performed at the University Children's Hospital in Belgrade, provides a complete insight and confirms the alarmingly high frequency of DKA at the time of diagnosis of T1DM in youth living in Belgrade (18). Similar worrisome DKA frequencies at T1DM onset were reported in other countries in the region, such as Croatia (31.3-41.7%) and Bosnia (48%) (21,22), although data from Montenegro showed a significantly lower incidence of 24.5% (23).

Many studies have demonstrated higher incidence of DKA at the time of T1DM diagnosis in patients aged < 5 years, with even higher rates in children younger than 2 years (17,24-27). Many authors suggest that higher incidence of T1DM in some countries is associated with a lower prevalence of DKA at the time of T1DM diagnosis, as the study from Finland that showed a relative reduction of DKA incidence over a period of 20 years, especially in the group of children younger than 5 years (28,29). However, a large study from 106 centeres in Germany and Austria failed to demonstrate changes in either incidence or severity of DKA during the study period 1995-2007, while a steadily high DKA prevalence of 43.9% was observed in a study conducted on a national level in France (30,31). In the present study, although slightly higher incidence of DKA was present in younger patients, and although the prevalence of severe DKA was also higher in this age group, these findings were not statistically significant and the DKA prevalence was fairly similar among the age groups. This emphasizes the urgency of public health actions aimed at prevention of DKA, not only in the youngest age group, but among school-aged children and adolescents as well.

When two consecutive 5-year periods were compared in the present study, the number of children and adolescents with new-onset T1DM was similar. The observed mild decline in the prevalence of DKA at the time of onset of T1DM in youth from 40.4% in the first 5-year period to 35.5% in the second, together with similar findings from the previous Belgrade study, could suggest that the public awareness of the T1DM has increased over the last couple of years (18). However, the rate of DKA at onset of T1DM in Belgrade youth is still alarmingly high and suggests the fact that public health preventive programs should be implemented in order to increase public awareness of T1DM in youth, as well as awareness amongst health care professionals.

Findings of the present study should be interpreted in the light of its acknowledged limitations. Impact of ethnicity, income status and family history were not assessed in the present study. Also, health insurance status was not assessed, though this should not have influenced findings in a significant manner, considering that free healthcare coverage is provided to all children in Serbia.

Conclusion

The presented findings confirm the alarmingly high rate of DKA at the onset of T1DM in Belgrade youth with no significant differences between different age groups. These findings emphasize the need for intensive public health preventive actions aimed at early T1DM diagnosis in all age groups, including school-aged children and adolescents, to reduce the rate of DKA, a potentially fatal T1DM complication.

References

1. Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes 1990-96. Arch. Dis. Child 1999; 81:318-23.
2. Sperling MA. Diabetic ketoacidosis in children: the problems continue (Editorial). Pediatr Diabetes 2006; 6:67-8.
3. Usher-Smith JA, Thompson M, Ercole A, Walter FM. Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. Diabetologia 2012; 55(11):2878-94.
4. Bui H,To T, Stein R,Fung K, Daneman D. Is diabetic ketoacidosis at disease onset a result of missed diagnosis? J Pediatr 2010; 156(3):472-7.
5. Neu A, Willasch A, Ehehalt S, Hub R, Ranke MB, Baden-Wuerttemberg DG. Ketoacidosis at onset of type 1 diabetes mellitus in children-frequency and clinical presentation. Pediatric diabetes 2003; 4(2):77-81.
6. Fritsch M, Schober E, Rami-Merhar B, Hofer S, Frohlich-Reiterer E, Waldhoer T, et al. Diabetic ketoacidosis at diagnosis in Austrian children: a population-based analysis, 1989-2011. J Pediatr 2013; 163(5):1484-8 e1.
7. Lansdown AJ, Barton J, Warner J, Williams D, Gregory JW, Harvey JN, et al. Prevalence of ketoacidosis at diagnosis of childhood onset Type 1 diabetes in Wales from 1991 to 2009

and effect of a publicity campaign. Diabetic medicine: a journal of the British Diabetic Association 2012; 29(12):1506-9.
8. Rewers A, Klingensmith G, Davis C, Petitti DB, Pihoker C, Rodriguez B, et al. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study. Pediatrics 2008; 121(5):e1258-66.
9. Kamal Alanani NM, Alsulaimani AA. Epidemiological pattern of newly diagnosed children with type 1 diabetes mellitus, Taif, Saudi Arabia. The Scientific World Journal 2013; 2013:421569.
10. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics 2014; 133(4):e938-45.
11. Levy-Marchal C, Patterson CC, Green A, Europe EASG, Diabetes. Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. European and Diabetes. Diabetologia 2001; 44 Suppl 3:B75-80.
12. Alvi NS, Davies P, Kirk JM, Shaw NJ. Diabetic ketoacidosis in Asian children. Archives of disease in childhood 2001; 85(1):60-1.
13. Hang JYH, Jalaludin MY, Mohamad Adam B, Fuziah MZ, WU LL, Rasat R, et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes mellitus in Malaysian children and adolescents. Malays Physician 20156; 10(3):11-8.
14. Soltesz G, Patterson CC, Dahlquist G. et al. Worldwide childhood type 1 diabetes incidence-what can we learn from epidemiology? Pediatr Diabetes 2007; (6):6-14.
15. Cherubini V, Skrami E, Ferrito L, Zucchini S, Scaramuzza A, Bonfanti R. et al. Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetology (ISPED). High frequency of diabetic ketoacidosis at diagnosis of type 1 diabetes in Italian children: a nationwide longitudinal study, 2004-2013. Sci Rep 2016; 6:38844.
16. Shaltout AA, Wake D, Thanaraj TA, Omar DM, Al-Abdul Razzaq D, Channanath A, et al. Incidence of type 1 diabetes has doubled in Kuwaiti children 0-14 years over the last 20 years. Pediatr Diabetes 2017; 18(8):761-6.
17. Jefferies C, Cutfield SW, Derraik JG, Bhagvandas J, Albert BB, Hofman PL, et al. 15-year incidence of diabetic ketoacidosis at onset of type 1 diabetes in children from a regional setting (Auckland, New Zealand). Sci Rep 2015; 5:10358.
18. Jesic MD, Jesic MM, Stanisavljevic D, Zdravkovic V, Bojic V, Vranjes M et al. Ketoacidosis at presentation of type 1 diabetes mellitus in children: a retrospective 20-year experience from a tertiary care hospital in Serbia. Eur J Pediatr 2013;172(12):1581-5.
19. Zoran Jančić. Census atlas 2011. Belgrade: The Statistical Office of the Republic of Serbia, 2011. Available at: http://popis2011.stat.rs/
20. Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N, Jain V. et al. ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatr Diabetes 2014; 15 Suppl 20:154-79. doi: 10.1111/pedi.12165.
21. Stipančić G, Sabolić La Grasta L, Šepec Požgaj M, Radica A, Skrabić V, Severinski S, et al. Regional difference in incidence and clinical presentation of type 1 diabetes in children aged under 15 years in Croatia. Croat Med J 2012; 53:141–8.
22. Tahirovic H, Toromanovic A, Bacaj D, Hasanovic E. Ketoacidosis at onset of type 1 diabetes mellitus in children in Bosnia and Herzegovina: frequency and clinical presentation. J Pediatr Endocrinol Metab 2007; 20(10):1137-40.
23. Samardzić M, Terzic N, Popovic M. Diabetic ketoacidosis in children with newly detected type 1 diabetes in Montenegro from 1999 to 2008. Med Pregl 2012; 65(11-12):503-6.
24. Roche EF, Menon A, Gill D, Hoey H. Clinical presentation of type 1 diabetes. Pediatr Diabetes 2005; 6:79–83.
25. Lokulo-Sodipe K, Moon R J, Edge JA, Davies J H. Identifying targets to reduce the incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in the UK. Arch Dis Child 2014; 99, 438–42.
26. Oyarzabal Irigoyen M; García Cuartero B; Barrio Castellanos R; Torres Lacruz M; Gómez Gila AL; González Casado I, er al. Ketoacidosis at onset of type 1 diabetes mellitus in pediatric age in Spain and review of the literature. Pediatr Endocrinol Rev 2012; 9: 669–71.
27. de Vries L, Oren L, Lazar L, Lebenthal Y, Shalitin S, Phillip M. Factors associated with diabetic ketoacidosis at onset of Type 1 diabetes in children and adolescents. Diabet Med 2013; 30:1360–6.
28. Eurodiab, ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. Lancet 2000; 355:873–6.
29. Hekkala, A., Knip, M, Veijola, R.

Ketoacidosis at diagnosis of type 1 diabetes in children in northern Finland: temporal changes over 20 years. Diabetes Care 2007; 30:861–6.
30. Neu A, Hofer SE, Karges B, Oeverink R, Rosenbauer J, Holl RW; DPV Initiative and the German BMBF Competency Network for Diabetes Mellitus. Ketoacidosis at diabetes onset is still frequent in children and adolescents: a multicenter analysis of 14,664 patients from 106 institutions. Diabetes Care 2009; 32:1647–8.
31. Choleau C, Maitre J, Filipovic Pierucci A, Elie C, Barat P, Bertrand AM, et al. Ketoacidosis at diagnosis of type 1 diabetes in French children and adolescents. Diabetes Metab 2014; 40:137-42.

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RAZLIKE U SEKSUALNOM PONAŠANJU IZMEĐU OBOLELIH OD SIFILISA I GONOREJE U BEOGRADU

DIFFERENCE IN SEXUAL BEHAVIOUR BETWEEN SYPHILIS AND GONORRHOEA CASES, BELGRADE

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SAŽETAK

Uvod/Cilj: Iako su sifilis i gonoreja prepoznate kao „stare" polne bolesti danas predstavljaju „nov" problem. Širom sveta opisan je porast obolevanja od sifilisa koji je često praćen HIV infekcijom, a usled pojave rezistencije gonokoka na sve veći broj antibiotika, gonoreja preti da postane neizlečiva bolest. Cilj ovog istraživanja je bio da se utvrde razlike između obolelih od sifilisa i gonoreje u odnosu na njihove demografske karakteristike i ponašanje.

Metode: U studiju preseka uključeni su oboleli od sifilisa i gonoreje koji su se tokom 2016. godine lečili u Gradskom zavodu za kožne i venerične bolesti u Beogradu.

Rezultati: U studiju je uključeno 278 pacijenta, 140 (50,4%) sa gonorejom i 138 (49,6%) sa sifilisom. U poređenju sa obolelim od gonoreje, pacijenti sa sifilisom su bili stariji, češće muškog pola i višeg obrazovnog statusa, kasnije su stupali u seksualne odnose – posle 20. godine, ređe su imali stalnog partnera, bili su homoseksualne ili biseksualne orijentacije, a tokom poslednjih šest meseci ćešće su praktikovali oralni i analni seks, kao i seks sa osobama iz inostranstva. Oboleli od sifilisa su ređe davali podatak o gonoreji u ličnoj anamnezi, ali su češće bolovali od sifilisa, hepatitisa B i bili su HIV pozitivni.

Zaključak: U poređenju sa obolelima od gonoreje pacijenti sa sifilisom su imali promiskuitetnije ponašanje, HIV pozitivan status i pripadali su populaciji muškaraca koji imaju seks sa muškarcima.

Ključne reči: sifilis, gonoreja, muškarci koji imaju seks sa muškarcima, HIV

SUMMARY

Intoduction/Aim: Although syphilis and gonorrhoea are "old" sexually transmitted diseases they have become a "new" problem: syphilis resurgence is noticed worldwide and it is followed by HIV co-infection, while drug-resistant gonorrhoea could be potentially untreatable infection. The aim of this study was to identify any differences between syphilis and gonorrhoea cases in regard to their demographic characteristics and behaviour.

Methods: In this cross-sectional study, data were collected from consecutive syphilis and gonorrhoea cases registered at the City Institute for Skin and Venereal Diseases in Belgrade in 2016.

Results: The study included 278 cases, 140 (50.4%) with gonorrhoea and 138 (49.6%) with syphilis. In comparison with gonorrhoea patients, syphilis patients were older, more frequently males with higher education, had their first sexual intercourse later, at 20+ years of age, less frequently had a permanent sexual partner, were more frequently homosexual or bisexual, and during the last 6 months had more frequently anal sex and oral-anal sex, as well as sex with a foreigner. They also had gonorrhoea in their personal history less frequently, but more frequently syphilis and hepatitis B infection, and they were more frequently HIV positive.

Conclusion: In comparison with gonorrhoea cases, patients with syphilis were more frequently men who have sex with men with more pronounced risk behaviour and HIV co-infection.

Keywords: syphilis, gonorrhoea, men who have sex with men, HIV

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Uvod

Polno prenosive infekcije predstavljaju važan javno zdravstveni problem zbog velikog broja obolelih i čestih komplikacija po reproduktivno i opšte zdravlje stanovništva. Tokom 2012. godine procenjeno je da je u svetu bilo 357 miliona novoobolelih sa jednom od četiri izlečive polne bolesti – hlamidijazom, gonorejom, trihomonijazom i sifilisom, a od toga 78 miliona obolelih od gonoreje i 5,6 miliona obolelih od sifilisa među osobama starosne dobi od 15 do 49 godina (1).

Gonoreja i sifilis su česte bakterijske infekcije čije je prijavljivanje obavezno u Republici Srbiji. U periodu od 2010. do 2016. godine incidencija sifilisa u Beogradu je porasla za 227,5% (sa 2,25/100.000 u 2010. godini na 5,12/100.000 u 2016. godini), a gonoreje za 162,5% (sa 2,56/100.000 u 2010. godini na 4,16/100.000 u 2016. godini) (2).

Iako se ove bolesti najčešće prenose seksualnim putem sifilis ima veću transmisivnost od gonoreje, jer se prenosi i putem krvi i vertikalnom transmisijom (3). Oba oboljenja su praćena ozbiljnim komplikacijama. Nelečena cervikalna gonoreja vodi do zapaljenskog oboljenja male karlice, ektopične trudnoće i infertiliteta (4), dok sifilis predstavlja sistemsko oboljenje sa neurološkim i kardiovaskularnim komplikacijama, a infekcija u trudnoći može biti povezana sa pobačajem, letalnim ishodom po plod ili, pak, rađanjem deteta sa znacima kongenitalnog sifilisa (5). Zbog kliničkih manifestacija bolesti (anogenitalne i oralne ulceracije) oboleli od sifilisa su u većem riziku od HIV infekcije (6).

Cilj ovog istraživanja je bio da se utvrde razlike između obolelih od gonoreje i sifilisa koji su dijagnostikovani i lečeni u Gradskom zavodu za kožne i venerične bolesti u Beogradu tokom 2016. godine u odnosu na njihove demografske karakteristike i ponašanje.

Metode

Studijom preseka obuhvaćeno je 278 pacijenata kod kojih je dijagnoza sifilisa i gonoreje postavljena u Gradskom zavodu za kožne i venerične bolesti u Beogradu između 1. januara i 31. decembra 2016. godine. Dijagnoze su postavljene na osnovu anamneze i kliničkog pregleda, a potvrđene su laboratorijskim analizama. Gonoreja je potvrđena izolovanjem Gram-negativnih intracelularnih diplokoka iz uretre muškaraca ili endocerviksa žena, dok su za potvrdu sifilisa korišćeni pozitivni treponemski (Treponema Pallidum Haemagglutination Assay – TPHA) i netreponemski (Venereal Disease Research Laboratory – VDRL) testovi (7,8).

Oboleli su popunjavali upitnik koji je obuhvatao osnovne demografske karakteristike ispitanika (pol, uzrast, bračno stanje, obrazovanje i zaposlenje), njihovu seksualnu orijentaciju, HIV status, seksualno ponašanje (uzrast pri prvom seksualnom odnosu, podatak o stalnom seksualnom partneru, seksualna aktivnost u proteklih šest meseci, broj seksualnih partnera tokom poslednjih 6 meseci, upotreba kondoma tokom poslednjih 6 meseci u zavisnosti od vrste seksualnog odnosa, seksualni odnos sa strancem, pod uticajem alkohola i droge tokom poslednjih 6 meseci), i ličnu anamnezu o polnim infekcijama.

U statističkoj analizi podataka korišćeni su $\chi 2$ test, Fišerov test i t-test. Izvođenje studije je odobreno od strane Etičkog komiteta Gradskog zavoda za kožne i venerične bolesti u Beogradu (br. protokola 2/2016).

Rezultati

U studiju je bilo uključeno 278 pacijenata od kojih je 140 (50,4%) bilo sa gonorejom, a 138 (49,6%) sa sifilisom (Tabela 1). Uzrast pacijenata kretao se između 19 i 39 godine (32,52 ± 10,08 godina), a većinu činili su muškarci (92,4%). Više od polovine (60,1%) je imalo osnovno ili srednje obrazovanje, a 56,8% je bilo zaposleno. U poređenju sa obolelima od gonoreje, pacijenti sa sifilisom su bili značajno češće muškarci ($p = 0,045$), starijeg uzrasta ($p < 0,013$), i višeg stepena obrazovanja ($p = 0,053$).

Tabela 1. Demografske karakteristike pacijenata sa sifilisom i gonorejom / Table 1. *Demographic characteristics of patients with gonorrhea and syphilis*

Karakteristike/ *Characteristics*	Oboleli od gonoreje/ *Gonorrhea cases* (N=140)	Oboleli od sifilisa/ *Syphilis cases* (N=138)	Ukupno/ *Total* (N=278)	p vrednost*/ *p value**
Uzrast (prosek ± SD)/ *Age (Mean± SD)*	31.04±9.77	34.03±10.21	32.52±10.08	0.013***
	Broj/No (%)	Broj/No (%)	Broj/No (%)	
Pol:/*Gender:*	125 (89.3)	132 (95.7)	257 (92.4)	
Muški/*Male*	15 (10.7)	6 (4.3)	21 (7.6)	0.067
Ženski/*Female*				
Bračni status:/*Marital status:*				
Neoženjeni/neudate				
Never married	114 (81.4)	114 (82.6)	228 (82.0)	
Oženjeni/udate				
Married	14 (10.0)	14 (10.1)	28 (10.1)	
Razvedeni				
Divorced	10 (7.1)	9 (6.5)	19 (6.8)	
Udovci/udovice				
Widowed	2 (1.4)	1 (0.7)	3 (1.1)	0.946**
Obrazovanje (broj godina škole):/ *Education (years spent in school):*				
≤ 12 godina/*years*	92 (65.7)	75 (54.3)	167 (60.1)	
> 12 godina/*years*	48 (34.3)	63 (45.7)	111 (39.9)	0.053
Zanimanje:/*Occupation:*				
Zaposlena lica/				
Employed	74 (30.0)	84 (60.9)	158 (56.8)	
Nezaposlena lica/				
Unemployed	42 (30.0)	42 (30.4)	84 (30.2)	
Izdržavana lica/				
Supported person	21 (15.0)	8 (5.8)	29 (10.4)	
Penzioneri/				
Retired	3 (2.1)	4 (2.9)	7 (2.5)	0.086**

*p vrednost prema hi kvadrat testu/**p value according to chi square test*; **p vrednost prema Fisher-ovom testu / ***p value according to Fisher's exact test*; ***p vrednost prema t-testu / ****p value according to t-test*.

Seksualno ponašanje ispitanika prikazano je u Tabeli 2. Više od polovine (58,6%) je prvi seksualni odnos imalo između 15. i 19. godine života, a 41,7% ispitanika je bilo heteroseksualne, 51,1% homoseksualne i 7,2% biseksualne orijentacije. Stalnog partnera je imalo 41,7% ispitanika. Tokom poslednjih 6 meseci 71,6% ispitanika je imalo seks sa nepoznatim partnerom, a skoro polovina (49,6%) je imala preko četiri seksualna partnera. Oralni seks je praktikovalo 94,2%, vaginalni 48,2%, analni 63,7%, a oro-analni 44,2% ispitanika. Jedna trećina ispitanika je imala seks sa osobom iz inostranstva. Tokom poslednjih 6 meseci seks sa prostitutkama imalo je 6,8% osoba, seks pod uticajem alkohola 36,7%, a seks pod uticajem droga 12,6% osoba. Čestu ili stalnu upotrebu kondoma prijavilo je 0,8% ispitanika tokom oralnog seksa, 32,1% tokom vaginalnog i 59,3% tokom analnog seksa. Između obolelih od sifilisa i gonoreje postojale su razlike u odnosu na njihovo seksualno ponašanje. Pacijenti sa sifilisom su značajno češće kasnije stupali u prvi seksualni odnos (p = 0,049), ređe su imali stalnog seksualnog partnera

(p = 0,020), praktikovali su homoseksualne ili biseksualne odnose (p < 0,001), i tokom poslednjih 6 meseci ređe su imali vaginalni seksualni odnos (p < 0,001), a češće analni (p= 0,001) i oro-analni seks (p = 0,016), kao i seksualne odnose u inostranstvu (p = 0,008).

Tabela 2. Seksualno ponašanje pacijenata sa gonorejom i sifilisom / *Table 2. Sexual behavior of patients with gonorrhea and syphilis*

Varijable/ *Variable*	Oboleli od gonoreje/ *Gonorrhea cases* (N=140) Broj/No (%)	Oboleli od sifilisa/ *Syphilis cases* (N=138) Broj/No (%)	Ukupno *Total* (N=278) Broj/No(%)	p vrednost*/ *p value**
Uzrast pri prvom seksualnom odnosu:/ *Age at first sexual intercourse:*				
<15	37 (26.4)	36 (26.1)	73 (26.3)	0.049
15-19	89 (63.6)	74 (53.6)	162 (58.6)	
20+	14 (10.0)	28 (20.3)	42 (15.1)	
Stalni seksualni partner:/ *Permanent sexual partner:*	68 (48.6)	48 (34.8)	116 (41.7)	0.020
Seksualna orijentacija/ *Sexual orientation*				
Heteroseksualna/ *Heterosexual*	85 (60.7)	31 (22.5)	116 (41.7)	<0.001
Homoseksualna/ *Homosexual*	47 (33.6)	95 (68.8)	142 (51.1)	
Biseksualna/ *Bisexual*	8 (5.7)	12 (8.7)	20 (7.2)	
Seksualni odnosi tokom poslednjih 6 meseci sa:/ *Sexual intercourse during last 6 months with:*				
Stalnim partnerom/ *Regular partner*	19 (13.6)	19 (13.8)	38 (13.7)	0.993
Povremenim partnerom/ *Casual partner*	21 (15.0)	20 (14.5)	41 (14.7)	
Nepoznatom osobom/ *Unknown new person*	100 (71.4)	99 (71.7)	199 (71.6)	
Broj seksualnih partnera u poslednjih 6 meseci:/ *Number of sexual partners during last 6 months:*				
1	21 (15.0)	22 (15.9)	43 (15.5)	0.143
2	32 (22.9)	18 (13.0)	50 (18.0)	
3	24 (17.1)	23 (16.7)	47 (16.9)	
4	18 (12.9)	14 (10.1)	32 (11.5)	
5+	45 (32.1)	61 (44.2)	106 (38.1)	

Oralni seks u poslednjih 6 meseci/ *Oral sex during last 6 months*	130 (92.9)	132 (95.6)	262 (94.2)	0.317
Upotreba kondoma tokom oralnog seksa:/ *Condom usage for oral sex during last 6 months:*				
Nikad/povremeno *Never/sometimes*	128 (98.5)	132 (100.0)	260 (99.2)	0.498
Često *Often*	2 (1.5)	0 (0.0)	2 (0.8)	
Vaginalni seks u poslednjih 6 meseci/ *Vaginal sex during last 6 months*	94 (67.1)	40 (29.0)	134 (48.2)	<0.001
Upotreba kondoma tokom vaginalnog seksa:/ *Condom usage for vaginal sex during last 6 months:*				
Nikad/povremeno *Never/sometime*	68 (72.3)	23 (57.5)	91 (67.9)	0.092
Često/uvek *Often/Always*	26 (27.7)	17 (42.5)	43 (32.1)	
Analni seks u poslednjih 6 meseci/ *Anal sex during last 6 months*	76 (54.3)	101 (73.2)	177 (63.7)	0.001
Upotreba kondoma tokom analnog seksa/*Condom usage for anal sex during last 6 months:*				
Nikad/povremeno *Never/Sometime*	35 (46.1)	37 (36.6)	72 (40.7)	0.207
Često/ uvek *Often/ Always*	41 (53.9)	64 (63.4)	105 (59.3)	
Oralno-analni seks u poslednjih 6 mesec/ *Oral-anal sex during last 6 months*	52 (37.1)	71 (51.4)	123 (44.2)	0.016
Seks sa strancem u poslednjih 6 meseci/ *Sex with foreigner during last 6 months*	36 (25.7)	56 (40.6)	92 (33.1)	0.008

* p vrednost prema hi kvadrat testu ili Fišerovom testu/ **p value according to chi square or Fischer's exact test.*

Tabela 3. Polno prenosive infekcije u ličnoj anamnezi pacijenata obolelih od gonoreje i sifilisa/ *Table 3. Sexually transmitted diseases in personal history of patients with gonorrhea and syphilis*

Varijable/ *Variable*	Oboleli od gonoreje/ *Gonorrhea cases* (N=140) Broj/No (%)	Oboleli od sifilisa/ *Syphilis cases* (N=138) Broj/No (%)	Ukupno/ *Total* (N=278) Broj/No(%)	p vrednost* /*p value**
Polno prenosive infekcije u ličnoj anamnezi/ *Sexually transmitted diseases in the personal history*	60 (42.9)	67 (48.6)	127 (45.7)	0.341
Gonoreja/*Gonorrhea*	31 (22.1)	18 (13.0)	49 (17.6)	0.046
Sifilis/*Syphilis*	6 (4.3)	24 (17.4)	30 (10.8)	<0.001
Gonoreja i sifilis/ *Both gonorrhea and syphilis*	3 (2.1)	4 (2.9)	7 (2.5)	0.722
Testiranje na HIV/ *Ever tested for HIV*	70 (50.0)	102 (73.9)	172 (61.9)	<0.001
HIV pozitivan status/ *HIV positive*	8 (5.7)	31 (22.5)	39 (14.0)	<0.001
Testiranje na hepatitis B (HBV)/ *Ever tested for hepatitis B virus (HBV)*	42 (32.8)	56 (46.3)	98 (39.4)	0.030
HBV infekcija/ *Ever had HBV infection*	5 (3.6)	24 (17.4)	29 (10.4)	<0.001
Vakcinisan za HBV/ *Vaccinated against HBV*	12 (8.6)	17 (12.3)	29 (10.4)	0.307
Testiranje na hepatitis C (HCV)/ *Ever tested for hepatitis C virus (HCV)*	44 (31.4)	55 (39.9)	99 (35.6)	0.142
HCV infekcija/ *Ever had HCV infection*	2 (1.4)	1 (0.7)	3 (1.1)	1.000

HIV – humani imunodeficijentni virus/ *HIV – human immunodeficiency virus*; *p vrednost prema hi kvadrat testu ili Fišerovom testu/**p value according to chi square or Fisher's exact test.*

Prema podacima iz lične anamneze, skoro svaki drugi ispitanik (45,7%) je već imao neku polnu prenosivu bolest (Tabela 3). To su najčešće bile gonoreja i sifilis, ili obe infekcije (30,9%), hepatitis B (10,4%), a samo 1,1% ispitanika imalo je hepatitis C infekciju. HIV infekciju je imalo 14% ispitanika. Procenat ispitanika testiranih na HIV je bio 61,9%, na hepatitis B 39,4%, a na hepatitis C 35,6%. Samo 10,4% ispitanika je primilo vakcinu protiv virusnog hepatitisa B. U poređenju sa obolelim od gonoreje, pacijenti sa sifilisom su značajno ređe imali gonoreju u ličnoj anamnezi ($p = 0,046$), a mnogo češće sifilis ($p < 0,001$), hepatitis B ($p < 0,001$) i HIV ($p < 0,001$). Oboleli od sifilisa su se i značajno češće testirali na HIV ($p < 0,001$) i hepatitis B infekciju ($p < 0,030$).

Diskusija

Prema rezultatima našeg istraživanja oboleli od sifilisa i gonoreje su se značajno razlikovali u više karakteristika. Pacijenti sa sifilisom, u poređenju sa obolelim od gonoreje, su bili značajno češće muškarci, stariji i višeg stepena obrazovanja, homoseksualne ili biseksualne orijentacije, a tokom poslednjih 6 meseci češće su praktikovali analni seks, oro-analni seks i seks sa osobama iz inostranstva. Takođe su češće bili HIV pozitivni i imali podatak u ličnoj anamnezi o sifilisu i hepatitis B infekciji, ređe su imali stalnog partnera, vaginalne seksualne odnose u toku poslednjih 6 meseci i podatak o gonoreji u ličnoj anamnezi.

Iako su sifilis i gonoreja „stare“ bakterijske infekcije, danas su postale „nov“ problem, jer se epidemija sifilisa udružena sa HIV infekcijom beleži širom sveta (9), a rezistentni sojevi gonokoka na lekove terapijskog izbora prete da ova bolest postane neizlečiva (10). Bakterijske polne bolesti olakšavaju prenošenje HIV infekcije naročito u populaciji muškaraca koji imaju seks sa muškarcima (MSM). Veći broj studija je opisao da je gonokokna infekcija nezavisni faktor rizika za HIV serokonverziju, dok sifilis zbog svojih epidemioloških i bioloških karakteristika olakšava transmisiju HIV infekcije (11-13). U isto vreme, visoko efikasna pre-ekspoziciona profilaksa, upotreba antiretroviralnih lekova od strane HIV negativnih osoba da bi se sprečilo dobijanje HIV-a, naročito među MSM populacijom, udružena je sa rapidnim padom upotrebe kondoma i porastom obolevanja od ostalih polnih infekcija (14).

Koinfekcija sifilisa i HIV- a i homoseksualna orijentacija naših ispitanika obolelih od sifilisa je u skladu sa podacima iz literature (15,16). Muškarci koji imaju seks sa muškarcima češće obolevaju od polnih infekcija u odnosu na heteroseksualne muškarce. Naime, stope HIV infekcije i ranog sifilisa kod homoseksualaca su četrdeset puta veće nego kod heteroseksualaca (17). Ovi podaci ukazuju da HIV inficirane osobe sa sifilisom u čijoj kliničkoj slici dominiraju genitalne ulceracije predstavljaju najvažnije prenosioce HIV-a. Stoga je bitno da se seksualno aktivne MSM osobe koje žive sa HIV-om najmanje jednom godišnje testiraju na sifilis.

Visoka učestalost polnih infekcija, veći broj seksualnih partnera i potencijalno ograničen pristup zdravstvenim ustanovama povećavaju rizik MSM populacije za nove polne infekcije (18). Oralni seks je česta praksa kod muškaraca, ali homoseksualne osobe ga češće praktikuju od heteroseksualnih, kao što smo opisali i u našem istraživanju (19,20). Veći broj studija je objavio da je oralni seks najčešći put prenošenja sifilisa među MSM populacijom (21,22). S druge strane, pre-ekspoziciona profilaksa praćena neupotrebom kondoma još više doprinosi porastu sifilisa među ovom grupacijom, zbog čega je neophodna ciljana zdravstvena edukacija vulnerabilnih osoba.

Karakteristike obolelih od gonoreje u našem radu, su da su to obično osobe heteroseksualne orijentacije, sa pozitivnom ličnom anamnezom za raniju gonokoknu infekciju i češćim praktikovanjem vaginalnog seksa, slažu se sa rezultatima studije sprovedene u San Francisku (23). Ranija istraživanja u našoj zemlji su pokazala da su faktori rizika za obolevanje od gonoreje bili niži stepen obrazovanja, mlađi uzrast, seks prvog dana po upoznavanju partnera, veći broj seksualnih partnera tokom poslednjih godinu dana i podatak o prethodnom obolevanju od gonoreje (24), i u skladu su sa rezultatima ove studije. Ozbiljan problem koji je prisutan širom sveta je pojava sojeva gonokoka koji su postali rezistentni i na cefalosporine, dosadašnju terapiju izbora u lečenju ovog oboljenja. Rezistentni sojevi su češće opisani među muškarcima koji imaju seks sa muškarcima (25). Brza dijagnostika oboljenja, uzimanje uzoraka sa većeg broja anatomskih lokacija (na primer sa rektuma i farinksa), nadzor, notifikacija partnera i rano efikasno lečenje mogli bi da spreče širenje rezistentnih sojeva gonokoka. Zdravstveno obrazovanje od ranog uzrasta i kasnija edukacija osoba pod rizikom za polne bolesti (seksualni radnici, muškarci koji imaju seks sa muškarcima, itd.) bile bi dodatne preventivne mere u naporima izmene rizičnih seksualnih ponašanja.

Zaključak

U poređenju sa obolelima od gonoreje, pacijenti sa sifilisom su češće bili homoseksualne orijentacije, praktikovali su rizičnija seksualna ponašanja i imali su HIV infekciju. Koordinirani nadzor, dostupnije zdravstvene službe, skrining i edukacija osoba pod rizikom, kao i rana dijagnoza i lečenje obolelih mogli bi smanjiti prenošenje i komplikacije ovih bakterijskih infekcija u našoj populaciji.

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Literatura

1. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. PLoS One 2015; 10(12): e0143304.
2. Centre for Disease Control and Prevention: Report of infectious diseases in Belgrade in 2016. Belgrade: City Institute of Public Health of Belgrade, 2017.
3. Garnett GP, Aral SO, Hoyle DV, Cates W, Anderson RM. The natural history of syphilis. implications for the transmission dynamics and control of infection. Sex Transm Dis 1997; 24(4): 185-200.
4. Hook EW III, Handsfield HH. Gonococcal infections in the adult. In: Holmes KK, Sparling PF, Mardh P, Stamm WE, eds. Sexually Transmitted Diseases. 4th ed. New York: McGraw Hill, 2008.
5. Sanchez MR. Syphilis. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, eds. Fitzpatrick's dermatology in general medicine, 6th ed. New York: McGraw-Hill, 2003.
6. Lynn WA, Lightman S. Syphilis and HIV: a dangerous combination. Lancet Infect Dis 2004; 4(7):456-466.
7. Centers for Disease Control and Prevention (CDC). STD Surveillance case definitions. Available at: http://www.cdc.gov/std/stats/casedefinitions-2014. pdf
8. Centers for Disease Control and Prevention (CDC). Recent changes to gonorrhea and syphilis case definitions: program impact. Available at: http:/www.cdc.gov/std/stats/casedef-programimpact-2014.pdf
9. Willeford WG, Bachmann LH. Syphilis ascendant: a brief history and modern trends. Trop Dis Travel Med Vaccines 2016; 2:20.
10. Alirol E, Wi Te, Bala M, Bazzo ML, Chen XS, Deal C, et al. Multidrug-resistant gonorrhea: a research and development roadmap to discover new medicines. PLoS Med 2017; 14(7): e1002366.
11. Galvis SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. Nat Rev Microbiol 2004; 2(1):33-42.
12. Zetola NM, Bernstein KT, Wong E, Louie B, Klausner JD. Exploring the relationship between sexually transmitted diseases and HIV acquisition by using different study designs. J Acquir Immune Defic Syndr 2009; 50(5):546-551.
13. Bernstein KT, Marcus JL, Nieri G, Philip SS, Klausner JD. Rectal gonorrhea and chlamydia reinfection is associated with increased risk of HIV seroconversion. J Acquir Immune Defic Syndr 2010; 53(4):537-543.
14. Nguyen VK, Greenwald ZR, Trottier H, Cadieux M,Goyette A, Beauchemin M, et al. Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. AIDS 2018; 32(4):523-530.
15. Paz-Bailey G, Meyers A, Blank S, Brown J, Rubin S, Braxton J, et al. A case-control study of syphilis among men who have sex with men in New York City: association with HIV infection. Sex Transm Dis 2004; 31(10): 581-587.
16. Wong W, Chew J, Kent C, Klausner J. Risk factors for early syphilis among gay and bisexual men seen in an STD Clinic: San Francisco, 2002-2003. Sex Transm Dis 2005: 32(7): 458-463.
17. Purcell DW, Johnson C, Lansay A, Prejean J, Stein R, Denning P, et al. Calculating disease rates for risk groups: estimating the national population size of men who have sex with men (abstract). National STD Prevention Conference. Atlanta, Georgia: CDC; 2010.
18. Spicknall IH, Gift TL, Bernstein KT, Aral SO. Sexual networks and infection transmission networks among men who have sex with men as causes of disparity and targets of prevention. Sex Transm Infect 2017; 93(5): 307-308.
19. Chandra A, Mosher WD, Copen C, Sionean C. Sexual behavior, sexual attraction, and sexual identity in the United States: Data from the 2006-2008 National Survey of Family Growth. Natl Health Stat Report 2011; 36: 1-36.
20. Bjekić M, Šipetić-Grujičić S, Vlajinac H, Nikolic A. Oral sex related knowledge and oral sex behavior among homosexual and heterosexual men in Belgrade: a cross-sectional study. Indian J Dermatol Venereol Leprol 2018; 84(5): 563-568.
21. Bjekić M, Šipetić-Grujičić S, Begović-Vuksanović B, Rafailović N, Vlajinac H. Syphilis resurgence in Belgrade, Serbia in the new millennium: an outbreak in 2014. Centr Eur J Public Health 2017: 25(4): 277-281.
22. Communicable Disease Surveillance

Centre. Increased transmission of syphilis in Brighton and Greater Manchester among men who have sex with men. Commun Dis Rep CDR Wkly 2000; 10: 383-386.
23. Barry PM, Kent CK, Klausner JD. Risk factors for gonorrhea among heterosexuals – San Francisco, 2006. Sex Transm Dis 2009;36 (2 Suppl): S62-6.
24. Bjekić M, Vlajinac H, Šipetić S, Marinković J. Risk factors for gonorrhoea: case – control study. Genitourin Med 1997; 73(6):518- 521.
25. Kirkcaldy RD, Zaidi A, Hook EW 3rd, Holmes KK, Soge O, del Rio C, et al. Neisseria gonorrhoeae antimicrobial resistance among men who have sex with men and men who have sex exclusively with women: The Gonococcal Isolate Surveillance Project, 2005–2010 Ann Intern Med 2013; 158: 321-328.

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PROGRAM SUZBIJANJA TUBERKULOZE U SRBIJI 2005-2015: REZULTATI I IZAZOVI

TUBERCULOSIS CONTROL PROGRAMME IN SERBIA 2005-2015: RESULTS AND CHALLENGES

Maja Stosic[1], Verica Jovanovic[1]

SAŽETAK

Najznačajniji napredak u suzbijanju tuberkuloze (TB) širom sveta tokom poslednje dve decenije postignut je razvojem i primenom strategija Svetske zdravstvene organizacije. Nacionalni program prevencije i suzbijanja TB u Srbiji sprovodi se u okviru Programa zaštite stanovništva od zaraznih bolesti. Cilj programa je bio da se smanji incidencija i smrtnost od TB i dostignu stope incidencije TB od 14 na 100.000 u 2014. godini. Implementacija je dovela do postizanja cilja programa, smanjujući stopu incidencije TB sa 32/100.000 u 2005. na 13/100.000 u 2015. Ojačani su kapaciteti u sistemu zdravstvene zaštite za dijagnostiku i lečenje TB osetljive na antituberkulotske lekove prve linije, uspostavljen je organizovan sistem za dijagnostiku i lečenje rezistentnih oblika bolesti, poboljšana je dijagnostika i lečenje udružene infekcije TB i HIV-om, smanjeno je opterećenje bolešću u zatvorima, uspostavljeno je aktivno pronalaženje obolelih od TB u populacijama pod posebnim rizikom, poboljšan je epidemiološki nadzor nad TB i uspostavljen je nadzor nad kvalitetom stručnog rada. Međutim, prevencija i suzbijanje TB u Srbiji još uvek nije na nivou razvijenih zemalja u Evropskoj uniji. Potrebno je da i dalje ostane na listi javnozdravstvenih prioriteta zbog prisustva oblika bolesti otpornih na lekove, udružene infekcije TB i HIV-om, sve većeg broja migranata iz područja sa velikim opterećenjem TB i mogućeg preokreta epidemioloških kretanja u vreme socijalno-ekonomske krize.

Ključne reči: tuberkuloza, preventivni programi, incidencija, rezistencija na lekove

SUMMARY

The most significant progress in tuberculosis (TB) control worldwide over the last two decades has been achieved through the development and implementation of World Health Organization strategies. The National TB Prevention and Control Programme in Serbia has been implemented under the Programme for Population Protection from Infectious Diseases. The goal of the programme was to reduce the incidence and mortality of TB and to reach the TB incidence rate of 14 per 100,000 in 2014. The implementation has led to achievement of the programme objective, reducing the TB incidence rate from 32/100,000 in 2005 to 13/100,000 in 2015. Capacities of the health care system to diagnose and treat TB sensitive to first-line anti-tuberculosis drugs have been strengthened, an organized system of diagnosis and treatment of drug-resistant forms of the disease was established, and management of TB and HIV coinfection was improved. The burden of the disease in prisons has been reduced, the active detection of TB cases in populations at special risk has been established, the epidemiological surveillance of TB has been improved and the surveillance has been established over the quality of professional work. However, TB prevention and management in Serbia is not yet at the level of the developed countries in the European Union. It still needs to remain on the list of public health priorities due to the presence of drug-resistant forms of the disease, the combined TB and HIV infection, the increasing number of migrants from areas with high TB burden and possible reversal of epidemiological trends during the social-economic crisis.

Keywords: tuberculosis, prevention programmes, incidence, drug resistance

Introduction

The most significant progress in tuberculosis (TB) control worldwide over the last two decades has been achieved due to the development and widespread implementation of the World Health Organization (WHO) strategies for TB control, which present a

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combination of technical and organizational components of diagnosis and treatment easily applicable in the population (1).

The implementation of the WHO's DOTS (Directly Observed Treatment Short Course) strategy from 1994 to 2005 strengthened the health sector and established basic conditions for diagnosis and treatment of TB, thereby contributing to reduction of TB transmission and preventing the development of resistant forms of the disease. Elements of this strategy represent the minimum necessary measures to control TB. WHO STOP TB strategy, implemented from 2006 to 2015, has contributed to the fight against drug-resistant TB, TB and HIV coinfection and promotion of research by strengthening the health system, expanding partnerships among all health care providers and organizations, civil society and the community (1,2).

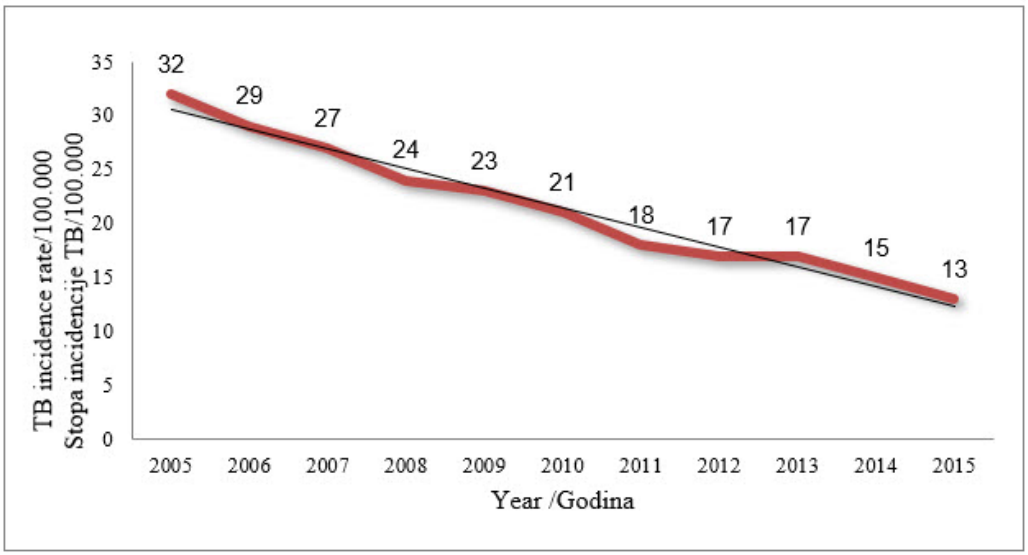
The TB Control Programme in Serbia is implemented within the Programme of Population Protection against Infectious Diseases (3). It is being implemented by health care institutions and other health care service providers, government administration, civil society organizations and communities (4).

Since 2003, the Ministry of Health of the Republic of Serbia has declared TB control to be one of its public health priorities and has begun implementing programmatic approach based on internationally effective strategies. From December 2004 to March 2015, National TB Control Programme in Serbia was supported by donations of the Global Fund to Fight AIDS, Tuberculosis and Malaria. The programme goal was to reduce the TB incidence and mortality by strengthening the implementation of the DOTS strategy, an increased level of interventions related to the management of multidrug-resistant tuberculosis (MDR TB) and TB/HIV coinfection programme activities, as well as by strengthening TB management in vulnerable populations, in order to reach TB incidence rate of 14 per 100,000 in 2014. The aim of this review was to examine whether the goals of the TB control programme in the Republic of Serbia were achieved.

Key programme performance indicators

Tuberculosis Control Programme implementation led to overachievement of the programme goal, by reducing the TB incidence rate from 32/100,000 in 2005 to 13/100,000 in 2015 and placing Serbia among the countries with low TB burden in the WHO European Region (Figure 1).

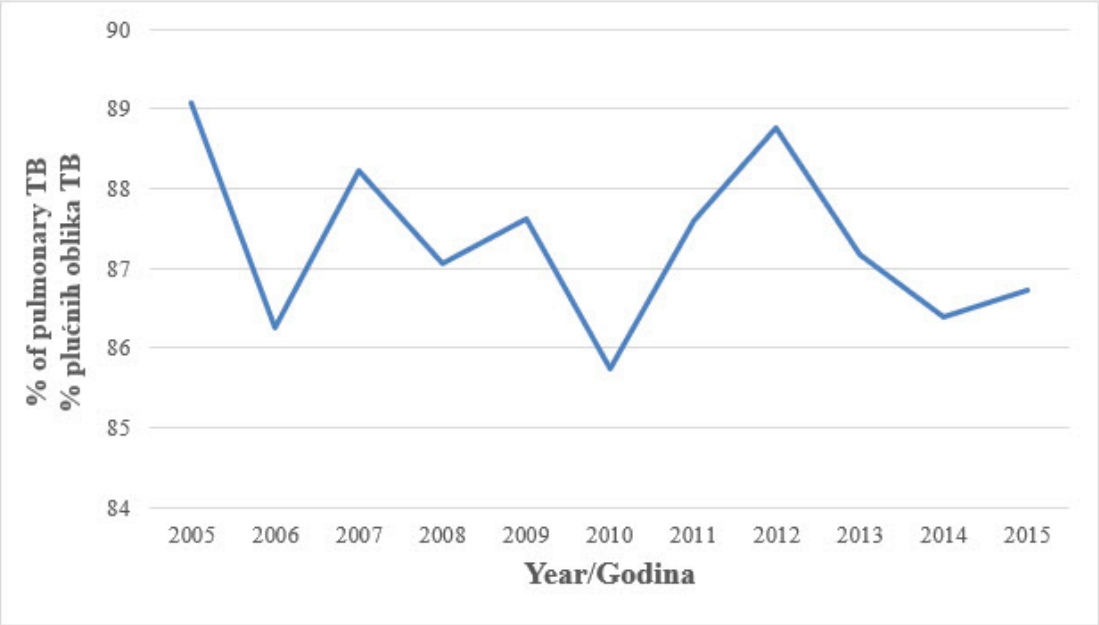
Figure 1.Tuberculosis incidence rate, Republic of Serbia 2005-2015 / Grafikon 1. Stopa incidencije tuberkuloze, Republika Srbija 2005-2015.



The number of TB patients decreased by 62%, from 2,378 registered in 2005 to 889 in 2015. Over the period of 11 years, there has been a constant gender ratio among patients, with male predominance (61%) over women (39%). The highest age-specific TB notification rate was in age group > 65 (24/100,000 in 2005 and 29/100,000 in 2015). The lowest age-specific TB notification rate was in age group 0-4 (2.3/100,000 in 2005 and 1.3/100,000 in 2015)

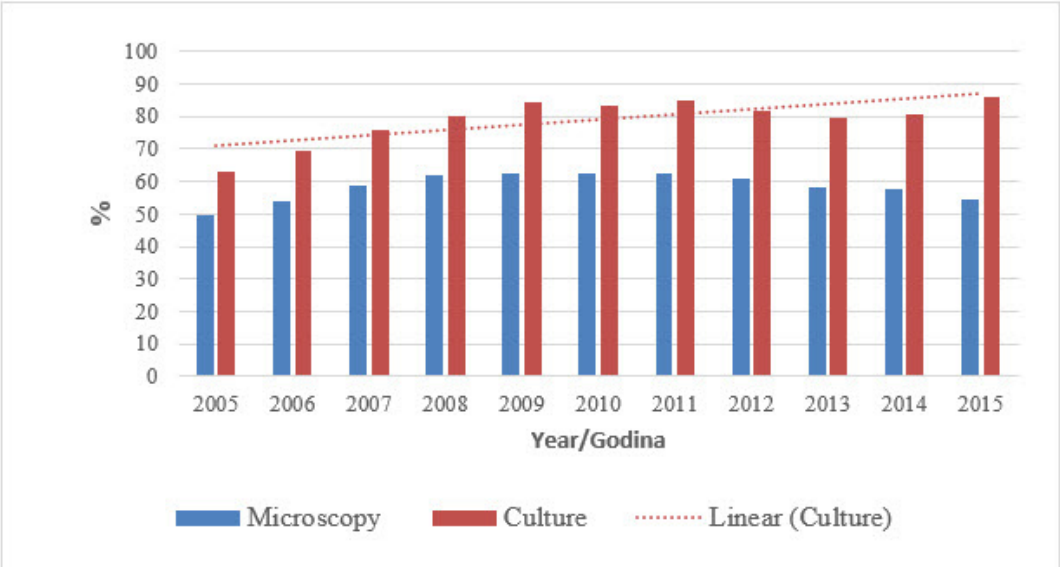
Pulmonary tuberculosis was diagnosed in 86-89% of cases, and the number has been declining over time (Figure 2).

Figure 2. Trends of proportions of pulmonary TB among total number of notified TB cases, Republic of Serbia 2005-2015 / Grafikon 2. Kretanje plućnih oblika TB u ukupnom broju prijavljenih slučajeva TB, Republika Srbija 2005-2015.



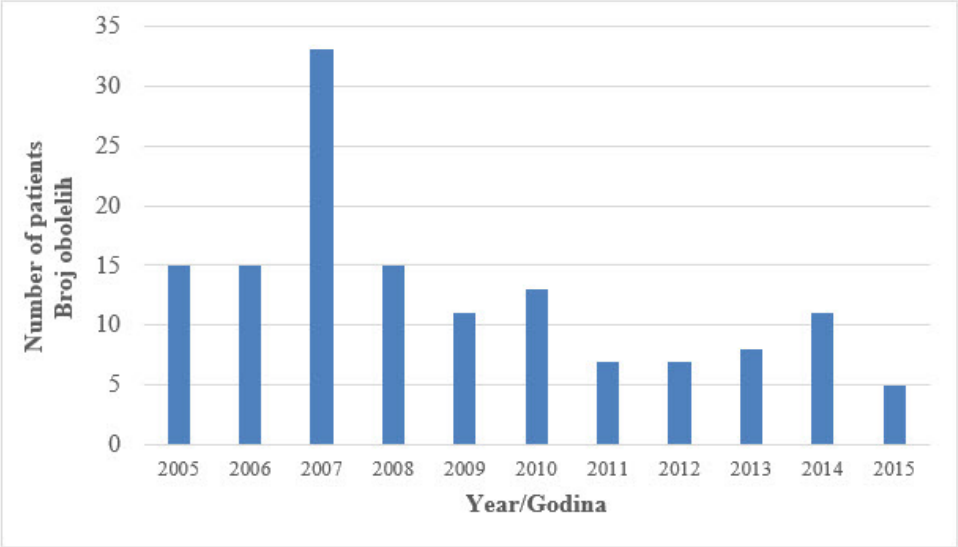
Total bacteriological confirmation among all cases ranged from 63% in 2005 to 75% in 2015 (Figure 3). Among extrapulmonary localisations, pleural (41-46%) and extrathoracic lymph nodes TB (22-23%) were most often registered.

Figure 3. Trends of proportions of bacteriological confirmation of pulmonary tuberculosis (by microscopy or by culture), Republic of Serbia 2005–2015 / Grafikon 3. Kretanje bakteriološke potvrđenosti plućne TB (mikroskopijom i kulturom), Republika Srbija 2005-2015.



Between 2005 and 2015, a total of 140 patients with multidrug-resistant tuberculosis were registered (Figure 4), accounting for 0.5 - 1.5% of the total annual number of registered tuberculosis patients.

Figure 4. Number of registered multi-drug resistant (MDR) TB patients in the Republic of Serbia 2005-2015 / Grafikon 4. Broj registrovanih obolelih od multirezistentne (MDR) TB, Republika Srbija 2005-2015.



Data on HIV status of TB patients have been available in the Republic of Serbia since 2010. The coverage of HIV testing among TB patients is very low, ranging from 1% in 2010 to 11% in 2015. The number of patients with the combined infection with TB and HIV in the same period ranged from 0.6% of the total annual registered number of TB patients in 2005 to 1.0% in 2015.

Treatment success rate over the last eleven years remains stable (Table 1), although TB mortality rate for all forms of TB was twice reduced, from 1.91 per 100,000 in 2005 to 0.89 per 100,000 in 2015.

Table 1. Outcome indicators of TB control programme, Republic of Serbia, 2005 to 2015 / Tabela 1. Ishodni pokazatelji programa kontrole TB, Republika Srbija 2005-2015.

Indicator / Pokazatelj	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Treatment success rate of new smear-positive TB cases (%)/Stopa uspeha lečenja novih sputum pozitivnih slučajeva TB (%)	82	83	85	85	86	86	84	82	79	80	83
Treatment success rate of laboratory confirmed MDR TB (%)*/Stopa uspeha lečenja laboratorijski potvrđenih slučajeva MDR TB*	-	-	-	-	55	76	71	57	75	89	80

TB-tuberkuloza; MDR-multirezistentna; *There are no MDR TB treatment outcome data for years 2005-2008 since organised MDR TB treatment in Serbia started in 2009/ Nema podataka o ishodima lečenja MDR TB u periodu 2005-2008. godine, jer je organizovano lečenje MDR TB u Srbiji počelo 2009. godine.

TB Prevention

The WHO recommends immunization with the Bacillus Calmette-Guérin (BCG) vaccine in countries with moderate and high incidence of pulmonary TB for infants to reduce the incidence of tuberculous meningitis and miliary tuberculosis in the first year of life. There is no evidence that BCG vaccination has an impact on TB incidence or control of the diseases in a future life (5). In the observed period, coverage of BCG vaccination ranged from 95-99%, representing very good vaccination coverage (6).

TB prevention is also performed by preventive treatment of latent TB infection – chemoprophylaxis, that includes administration of anti-TB medicines to persons at significant risk for tuberculosis (people living with HIV, adult and child HIV negative contacts, patients receiving anti-TNF therapy, patients on dialysis, those in process of preparation for transplantation and with silicosis) (7). Latent TB infection (LTBI) diagnosis and control in Serbia is a challenge, given the fact there is no organized data collection of diagnosed LTBI or on the administration of chemoprophylaxis, since the National Law on Population Protection against Infectious Diseases prescribes reporting active TB only (4).

Early detection of TB patients and coverage by the first line anti-TB drugs susceptibility testing

Early detection of patients and rapid initiation of treatment are the most effective measures to prevent the TB spread and ensure treatment success (1). In the last 11 years, the proportion of sputum smear-positive pulmonary forms of the disease has increased from 50% to 60% (6,8). This is the indicator of the capacity of the programme for early TB detection. The value of the indicator should not exceed 45%. This data indicates that patients are detected at a later stage of the disease when the likelihood of the occurrence of severe forms with a worse prognosis is greater. Furthermore, the likelihood of disease spread due to the prolonged period before treatment initiation is higher (9). This may indicate reduced access and availability of TB care in our country. From 2011-2013, within the reform of the health care system in Serbia, decentralization and status transformation of health care facilities and services were carried out. Previous “pillars” of TB control in Serbia, the so-called anti-TB dispensaries, have not been designated any more as special organizational units where the patients have direct access to the services. Instead, they have been associated with other specialized consultative services at the primary health care level or with the pulmonology departments of general hospitals. Moreover, in 2008, as a part of the patient centred approach in health care, the concept of ”chosen doctor” was introduced. The overall health of the patients, including early detection of TB has been under their responsibility. Direct access to TB services is thus disabled, except in Belgrade and Nis, where the Municipality institutes for TB and lung diseases still exist at the primary level of health care.

In the same period, the coverage by drug susceptibility testing for first-line anti-TB drugs increased 8-fold, with a peak value of 94% in 2014. There is no possibility of M. tuberculosis resistance to second-line anti-tuberculosis drugs (8).

Treatment of TB patients with support for the treatment of patients with drug-resistant TB

Tuberculosis treatment is being implemented through the use of standardized regimens in accordance with the national TB guidelines (10), and the treatment of resistant forms in accordance with the WHO guidelines for the treatment of drug-resistant TB with the individualized regimens based on drug resistance profile of the causative agent (11). Medicines for the treatment of extensively resistant forms of the disease are still not available in Serbia.

There have been no reported interruptions in the supply of first and second-line anti-TB drugs for the treatment of all forms of TB in previous years. Procurement of second-line anti-TB was performed from 2009 to 2013 within the Ministry of Health’s Tuberculosis Control Project from the funds donated by the Global Fund to fight AIDS, TB, and malaria. From 2014, the National Health Insurance Fund has undertaken the obligation of centralized procurement of drugs according to the newly developed legislation (12).

Support to 46 MDR TB patients throughout Serbia was provided within the project of the Ministry of Health until March 2015, in order to increase their compliance with the therapeutic regimen and to help them complete the prolonged treatment lasting up to 2 years (8).

Epidemiological surveillance of tuberculosis

According to National legislation (13), systematic collection of TB data is mandatory as a part of continuous routine surveillance of TB and is the basis for evidence-based assessment of TB programme performance. TB data have been collected in the last 11 years in two ways:

- By common notification form for data collection of all infectious diseases cases (basic data)
- By supplementary notification form where the detailed case-based TB data are collected in line with the WHO TB reporting form, developed in 2004 within the Global Fund TB project.

TB case definitions are clearly listed in the guidelines for TB doctors as a part of routine TB training in the country and are consistent with WHO guidelines (10,14). The first categorization of TB cases is usually performed at the time of completing the TB notification form, by a physician who diagnosed TB, based on medical investigations and medical records. Data from the TB notification form are further validated at the regional level by epidemiologists and pulmonologists before being entered into case-based electronic data collection system. The third data quality checks are usually performed at the central (national) level by automatic checks for duplicates, missing records and consistency during the process of data clean-up before data analysis, since central level receive copies of all case-based TB notification forms. The reliability of the data can be considered to be satisfactory.

Epidemiological investigation and contact tracing

The coverage by examinations and contact tracing in the observed period decreased from 90% in 2005-2007 to 86% in 2015. The number of TB patients identified by contract tracing is decreasing as well, from 20-30 in the period from 2005-2010 to 12 in 2015, most likely due to the abolishment of TB dispensaries (8). In order to mitigate the consequences of organizational transitions within the healthcare system and to maintain the level of TB prevention in the population, there is a need for improvement in epidemiological investigation of TB cases and an increased coverage of contact tracing by priority groups based on the characteristics of the index case and the level of exposure, by the competent services within the network of the public health facilities in line with the legislation (4).

TB control in vulnerable populations

Due to implementation of the Global Fund grant programme from 2005 to 2015, active TB detection has been performed among prisoners, people living with HIV (PLHIV), users of opioid substitution therapy (OST), soup kitchen users, sex workers and injecting drug users. Interventions among prisoners, PLHIV and OST users have been performed by health service, while the interventions in other vulnerable populations have been provided by the Red Cross of Serbia and other civil society organizations. In prisoners, PLHIV, and users of substitution therapy, over 95% of persons with TB symptoms have been covered by medical examinations. Active TB screening among prisoners has been performed by chest-X ray examination while among other populations by symptom-based questionnaire. Interventions among prisoners and soup kitchen users did not turn to be cost-effective since they covered a population above 20,000 and detected only up to 10 TB patients (8).

This high level of interventions stabilised TB burden among previously listed population groups. On the other hand, the level of active interventions among migrant populations has been very low. Serbia is one of the transit countries for migrants heading to the European Union (EU). The number of arrivals that reaches 2,500 - 3,000 persons per day puts severe pressure on the existing reception capacities of the country. The majority of the refugees come from Syria (67%), Iraq (15%) and Afghanistan (7%), countries significantly more affected with TB and MDR-TB than Serbia (15). The immigration has been identified as a significant factor for increased prevalence of TB and MDR-TB in European countries (16). Therefore, efforts should be made to increase TB case detection among migrant populations, with special emphasis on those from countries with dominant MDR-TB strains (17).

Quality control of professional work

The plan of regular external quality control of healthcare institutions is created by the Institute of Public Health of Serbia, while financial resources are provided from the budget of the Republic of Serbia based on the annual work plan. According to the existing

legislation (18,19), the quality of professional work is supervised at the level of the institution as a whole, and not in relation to the disease programme. In the period 2006-2014, external quality control of professional work was carried out in each pulmonology service and microbiology laboratory performing TB diagnostics at the district level, based on the internationally recognized strategies. It contributed to the implementation of the unique professional doctrine and continuity in the quality of all segments of professional work (8). As part of our country's international cooperation with the European Centre for Disease Control in Stockholm, the quality control of the National Reference Laboratory (NRL) for TB is carried out annually. In the observed period, the results showed 100% agreement with the findings of the European Centre (8).

Continuous medical education for health care professionals

Education and training are essential for sustainable TB control programmes (1). The training should not only be limited to health professionals; it is also important to extend it to all partners in programme implementation, the decision-makers who have an impact on health education plans, as well as the public. These groups need to be aware of the existence of TB and its elimination as a public health problem and to understand the interventions required to achieve that (2).

The Ministry of Health of the Republic of Serbia and the Medical Schools are responsible for comprehensive training in the field of TB at undergraduate and postgraduate level of education of health care providers, as well as for their continuous education during their TB-related practice. They are also responsible for the continuous health resource planning and profiling in order to ensure the appropriate numbers of health care professionals, with adequate knowledge, skills and motivation to provide services to persons in need in a timely manner.

In the context of the reform of the health care system and discontinuation of the specialization in pneumophysiology, the need for continuous development of human resources at the primary health care level is increasing (20).

Development of professional guidelines

In addition to staffing, facilities and equipment, the pillars of the implementation of health programmes are continuous development and revision of strategic framework documents and professional guidelines. Resource allocation within the health sector budget depends on the strategic interventions, while the quality of services depends on the guidelines. The revisions should be based on the results of continuous monitoring and evaluation of the programme, the definition of priority activities and interventions for the next period, and in compliance with the latest internationally agreed recommendations and proven successful practices.

In the period 2005-2015, during the implementation of the Ministry of Health project, 11 publications were issued (8).

Research and innovations

The continuous research is needed to ensure evidence-based decision-making, the introduction of new diagnostic methods, medicines, vaccines and effective programme implementation (2). Due to financial shortcomings in our country, the limited funds are allocated for that purpose.

To increase allocations for TB research, awareness of all key stakeholders (scientists, public health professionals, programme managers, financial partners, decision-makers and civil society representatives) needs to be strengthened on the importance of implementing tuberculosis research at the local and national level or to contribute to global TB research through inclusion in international research. From 2006 to 2014, four researches were performed within the national TB programme, all financed from the Global Fund donation (8).

Conclusion

During the observed 11 years period, the burden of TB in Serbia has significantly decreased due to the implementation of the National TB Control programme based on WHO DOTS and STOP TB strategy. Capacities in the health care system for diagnostics and treatment of drug-susceptible TB were strengthened, organized system for the diagnosis and treatment of drug-resistant forms of diseases was established, management of TB and HIV coinfection was

improved, good disease control in prisons was established, active TB case finding for populations at special risk and epidemiological surveillance of TB was improved and quality control of professional work was established.

Good disease control is the result of more than a decade of well-coordinated programmatic measures but also of the good basic capacities of the anti-tuberculosis health service built in the Republic of Serbia since the early 1920s.

The comprehensive task of TB elimination as a public health problem requires further expansion of the scope of preventive, diagnostic and therapeutic interventions. In practical terms, the continuous progress in control of this disease beyond 2015 requires more intensive activities within and outside the TB programme, both inside and outside the health sector. From 2012 to 2014, the recent WHO End TB Strategy was developed for the period 2016-2035, with the aim of contributing to the elimination of tuberculosis as a public health problem, reaching the Global Millennium Development Goals beyond 2015 and Sustainable Development Goals.

However, TB control in Serbia is still not at the level of the developed countries in the European Union. It is necessary to keep it on the list of public health priorities due to the presence of drug-resistant forms of the disease, coinfection with TB and HIV, increasing number of migrants from the high TB burden areas and possible reversal of epidemiological trends due to the social-economic crisis.

References

1. The Stop TB Strategy. Building on and enhancing DOTS to meet the TB-related Millennium Development Goals. WHO/HTM/TB/2006.368 Geneva: World Health Organization and Stop TB Partnership, 2006.
2. World Health Organization: Implementing the end TB strategy: the essentials. Geneva, Switzerland: WHO, 2015.
3. Regulation on Public Health Protection against Infectious Diseases ("Official Gazette of the RS", No. 29/2002).
4. Law on the Protection of the Population from Infectious Diseases ("Official Gazette of the RS", No. 125/2004).
5. Fine PEM, Cameiro IAM, Milstein JB, Clements CJ. Issues relating to the use of BCG in immunization programs: a discussion document. Geneva: World Health Organization, 1999.
6. Public Health Institute of Serbia (2005-2015) Reports on communicable diseases in the Republic of Serbia for 2005-2015. Available: http://www.batut.org.rs/
7. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: WHO, 2018.
8. Ministry of Health of the Republic of Serbia. Report on TB in Serbia 2005-2015. (2006-2015).
9. Ait-Khaled N, Alacron E, Armengol R, Bissell K, Boillot F, Caminero JA, et al. Management of tuberculosis: a guide to essentials of good practice. Paris, France: International Union against Tuberculosis and Lung Disease, 2010.
10. Radosavljevic Asic G, Rebic P, Kuruc V: Methodological guidelines for tuberculosis prevention and control. Belgrade: Ministry of Health of the Republic of Serbia; 2009.
11. Guidelines for programmatic management of drug-resistant tuberculosis: 2011 update. WHO/HTM/TB/2011.6. Geneva: World Health Organization, 2011.
12. Regulation on Planning Goods and Services by Centralised Public Procurement ("Official Gazette of the RS", No. 23/2013)
13. Rulebook on Reporting Infectious Diseases and Other cases established by the Law on Protection of the Population from Infectious Diseases ("Official Gazette of the RS, No. 125/04)
14. Definitions and reporting framework for tuberculosis – 2013 revision. WHO, 2014.
15. Situation and needs of internally displaced persons. Commissariat for refugees and migration of the Republic of Serbia. 2018. Available at: https://www.unhcr.org/see/wp-content/uploads/sites/57/2018/12/Situation_and_Needs_of_IDPs_2018_ENG.pdf
16. European Centre for Disease Prevention and Control: Tuberculosis surveillance and monitoring in Europe 2016. Stockholm, Sweden: ECDC, 2016.
17. Abarca Tomás B, Pell C, Bueno Cavanillas A, Guillén Solvas J, Pool R, Roura M. Tuberculosis in Migrant Populations. A Systematic Review of the Qualitative Literature. PLoS ONE 2013;8(12): e82440.
18. Strategy for the Continuous Improvement of the Quality of Health Care and Patient Safety ("Official Gazette of the RS", No. 15/2009). Available at: http://pravni-skener.org/pdf/sr/baza_propisa/77.pdf
19. Rulebook on quality control of professional work of health institutions, private practice, health workers and health assistants ("Official

Gazette of the RS", No. 35/2011). Available at: http://www.pravnoinformacionisistem.rs/SlGlasnikPortal/eli/rep/sgrs/ministarstva/pravilnik/2011/35/1/reg
20. Stošić M, Lazarević N, Kuruc V, Ristić L. Assessment of the role of primary health care in tuberculosis control in Serbia. Med Pregl 2015; 68(9-10):331-5.

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DOJENJE IZ UGLA DEČJEG STOMATOLOGA

BREASTFEEDING – THE PERSPECTIVE OF PAEDIATRIC DENTIST

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SAŽETAK

Savremene preporuke Evropske i Američke akademije dečjih stomatologa i Međunarodnog udruženja dečjih stomatologa savetuju postepeni prekid dojenja nakon nicanja mlečnih zuba kako bi se smanjio rizik od nastanka karijesa ranog detinjstva (KRD). Sa druge strane, preporuke Svetske zdravstvene organizacije, preporuke Američke akademije pedijatara i stručnjaka iz oblasti ishrane prepoznaju brojne kratkoročne i dugoročne pozitivne efekte dojenja i podržavaju isključivo dojenje do uzrasta od šest meseci, a zatim postepeno uvođenje čvrste hrane sa nastavkom dojenja uz neograničeno i dojenje na zahtev do druge godine deteta i duže. Cilj ovog preglednog rada je bio da se analiziraju savremeni podaci u literaturi o uticaju dojenja na nastanak KRD, kako bi se doprinelo formiranju jedinstvenog stava i pružila jasna informacija majkama kako prevenirati KRD. Na osnovu pretraživanja Pub Med baze podataka, uočava se da postoji povezanost između dojenja i KRD, ali nije dovoljno argumentovano koje su najbolje mere u prevenciji karijesa. Imajući u vidu poznate pozitivne efekte dojenja, smatra se da je preporučljivo pratiti savremene pedijatrijske preporuke koje savetuju neograničeno dojenje koliko god to uzajamno prija majci i detetu. Ipak, potrebno je imati u vidu neophodnost ranih preventivnih poseta dečjem stomatologu i edukacije zdravstvenih radnika radi adekvatnih i blagovremenih saveta o higijeni usne u duplje i ishrani kako bi se izbegao nastanak karijesa ranog detinjstva i omogućilo blagovremeno dijagnostikovnje inicijalnih lezija. Neophodna su dalja istraživanja u ovoj

SUMMARY

Current recommendations by the European Academy of Paediatric Dentistry, American Academy of Paediatric Dentistry, and International Association of Paediatric Dentistry advocate weaning from breast milk and avoiding unrestricted breastfeeding after the eruption of primary teeth in order to lower the risk of early childhood caries (ECC). However, World Health Organization, American Academy of Paediatrics and nutritional recommendations support exclusive breastfeeding up to six months of age, following continued breastfeeding along with appropriate complementary foods, favouring unrestricted and prolonged breastfeeding even beyond the age of two. The purpose of this review is to discuss current data in the literature regarding the association between breastfeeding and ECC in order to address this problem and to provide consistent recommendations. PubMed search revealed possible link between breastfeeding and ECC, however without evidence strong enough to establish the appropriate oral health preventive recommendation. Having in mind known benefits of breastfeeding, it is advisable to adhere to current paediatric guidelines which promote unrestricted breastfeeding as long as it is mutually desired by mother and child. This recommendation doesn't exclude but complements the prevention and timely treatment of ECC. Furthermore, there is a need to highlight the importance of education of parents and health care providers about the ECC risk factors, identification of initial lesions and consequences. Further research regarding this issue is

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needed.
Keywords: breastfeeding, dental caries, infant.

Introduction

Breastfeeding brings numerous benefits to both mothers and children, but it has social and economic effects on families and societies, too (1). Breastfeeding positively affects mothers' health improving healing of childbirth trauma and lowering the risk of obesity, osteoporosis, breast and ovarian cancer, etc. (2). Furthermore, breastfeeding improves infant's emotional and psychological development, wellbeing, and general health (decreasing the risk of acute and chronic diseases such as asthma, pneumonia, bronchiolitis, acute otitis media, allergies, diarrhoea, gastroenteritis, diabetes mellitus, leukaemia, atopic dermatitis and sudden infant death syndrome) (3). In addition, evidences from the research indicate that breastfed babies are less likely to become obese in adulthood (4).

World Health Organization, American Academy of Paediatrics and nutritional recommendations regarding breastfeeding are clear – starting breastfeeding within the first hour of life, supporting exclusive breastfeeding up to six months of age, followed by continued breastfeeding along with appropriate complementary foods, favouring unrestricted and prolonged breastfeeding even beyond the age of two (5-7).

However, paediatric dental recommendations suggest that prolonged, unrestricted, and frequent breastfeeding (more than 7 times a day) after the first birthday, especially night feedings, affect oral health and favour the development of early childhood caries (ECC) (8-12). Some studies also identified sleeping with the nipple in the mouth as a risk factor for ECC (13). Accordingly, gradual weaning and avoiding unrestricted breastfeeding after the eruption of the first primary teeth by 12th to 14th month of age is recommended (9).

ECC represents one of the most common diseases in paediatric population (14,15) leading to reduced quality of life due to pain, impaired eating, social skills, loss of sleep, causing distress, altered behaviour and disturbances in child's nutritional status and development (16). Likewise, ECC might cause repeated prescription of antibiotics, emergency room visits and even hospitalization (17).

Globally present and traditionally opposing opinions between paediatricians and paediatric dentists result in confusion, since nursing mothers are unable to get clear and straightforward guidelines (18). Therefore, there is a strong need to clarify the association between breastfeeding practices and the occurrence of ECC. The aim of this review was to analyze the results from currently available studies discussing breastfeeding effect on oral health.

Methods

A PubMed search using combinations of keywords related to infant breastfeeding pattern (breastfeeding, nursing, feeding, children, infant) and early childhood caries (early childhood caries, nursing caries, rampant caries, baby bottle caries, decay, etc.) was performed based on studies published in English before September 2019. All articles with available full text were analyzed; studies investigating the association of breastfeeding and ECC were selected and divided in two large groups based on positive or negative association between breastfeeding and ECC. Furthermore, articles were analyzed according to their study methodology.

Evidence suggesting a link between ECC and breastfeeding

Cariogenic potential of human breast milk was proposed when investigators observed higher levels of carbohydrates and lower levels of calcium, phosphorus and proteins compared to bovine milk (19-22). Incubation of human milk with saliva caused significant drop in pH level (from 6.44 to 4.57), suggesting possible occurrence of demineralization if contact with enamel lasted for 8 hours per night during 6-day immersions (23).

Epidemiological cross-sectional studies reported higher occurrence of caries in breastfed children and the necessity to educate parents to stop breastfeeding after 12th to 18th month (24-28). Positive association between breastfeeding and caries was confirmed by observation of infants who were breastfed for more than 13 months (29), more than 18 months (30-32) and more than 24 months (33). Furthermore, follow up of a cohort who was still breastfed at 18th and at 24th month of age showed higher frequency of ECC in breastfeeding-on-demand group (34). Another cohort study that involved Southeast Asian

participants aged 25 to 30 months showed that prevalence of ECC was higher in a group of children who were breastfed more than twice during the night (35). Peres et al. stated that "breastfeeding between 13 and 23 months had no effect on dental caries, but breastfeeding after 24 months of age increased risk for severe ECC at the age of five" (36), but there is "caution needed over breastfeeding advice" (37) especially considering that almost half of the cohort sample was bottle fed at the age of five and that oral behaviours were not analyzed.

Breastfeeding beyond 12 months of age and bottle feedings on demand with any carbohydrate beverages including human milk are considered ECC risk factors because frequent or prolonged contact with dental surfaces may contribute to evolution of lesions (12,38-40). In Lancet series on breastfeeding, caries was described as the only poor health outcome in prolonged breastfeeding after first birthday (41).

Evidence opposing a link between ECC and breastfeeding

Experimental studies demonstrated that human breast milk contains several components involved in neonatal host defence (lysozyme, lactoferrin, oligosaccharides and IgA antibodies) that prevents infections during early infancy and interfere with cariogenic streptococcal colonization of oral cavity (42). Furthermore, the presence of phosphate and proteins in human breast milk enables light buffering capacity. Interestingly, the experimental results confirmed acid neutralization potential of human milk even after primary teeth were soaked in it for 12 weeks – on the other hand, when 10% sucrose was added, demineralization occurred after 3.2 weeks (43).

Having in mind the physiological mechanism of suckling that involves using intraoral vacuum, expressing the milk at the edge of transition of soft palate into hard palate, and constant moving of fluid towards pharynx without stagnation – prolonged exposure of dental surfaces is almost impossible (44). On the other hand, during the bottle-feeding, artificial nipple releases the milk or formula into the frontal parts of the mouth and enables pooling of liquid in the mouth and exposure of the dental surfaces which favours occurrence of ECC.

Epidemiological research involving children breastfed up to 21.5 months showed low rates of ECC (45-47). On the other hand, sugary snacks between meals were strongly related to poor oral health (48,49). Follow up of the cohort from birth to nine years highlighted breastfeeding shorter than 6 months as a significant risk factor for ECC, due to bottle feeding (48,50). The largest randomized trial in the field (involving 13,889 children followed from the postpartum hospital stay until the end of the first year of life), showed the absence of association between prolonged and exclusive breastfeeding and ECC (51).

Studies that involved nationally representative samples in the USA with strong methods using regression model, adjusting for confounding variables and categorizing breastfeeding duration and type, could not determine any association between length of breastfeeding and ECC (52,53). Furthermore, matching for age, race, gender, and social class in 109 children with ECC with 109 healthy children confirmed that ECC occurrence was unrelated to length or type of feeding (46). Considering complicated aetiology of ECC, applying hierarchical approach in order to eliminate potential confounders showed no association of breastfeeding with poor oral health, even with longer breastfeeding exposure (54).

Some studies confirmed that up to 24 months breastfeeding did not affected oral health, but others showed less association between breastfeeding longer than 24 months of age and risk for ECC (55).

Advantages and disadvantages of different types of studies

Current literature data revealed possible link between breastfeeding and ECC, however without evidence strong enough for the appropriate oral health preventive recommendation to be provided.

Multi causal aetiology of ECC that involves plethora of micro, meso and macro level factors makes research of the association between ECC and breastfeeding inconclusive. Therefore, the use of adjustment for confounding variables related to ECC development brings needed strong research evidence (18,53,54). The use of multivariate risk model makes precise predictions related to ECC risk, but the analysis that involves only one factor such as the relationship with breast or bottle-feeding showed poor accuracy and limited strength of evidence (56).

When analyzing how breastfeeding affects oral health, it is important to consider

and understand differences between the following forms of breastfeeding: exclusive (breastfeeding excluding any other drinks or foods, except vitamins, oral rehydration solution, supplements and medicines) , unrestricted (on-demand or ad-libitum or on cue –baby is breastfed whenever in need) (57), predominant (receiving water, tea or fruit juice besides breast milk) (58), or partial (some meals are breast milk, and some are solids) (58).

The term "prolonged breastfeeding" has been differently defined – from up to six months (59), to more than one year (46, 51, 60), 18 months (30-32) or 24 months (33). There is a strong need for the use of the Index of Breastfeeding Status (61) in oral health research in the future, since this index was created in order to precisely determine the effect of breastfeeding on health outcomes, so the use of this tool is required for the analysis of oral health outcomes, too.

Frequent breastfeeds after 12 to 18 months of age might favour the development of inadequate dietary habits, such as prolonged, frequent and in-between-meal consumption of sugary snacks or drinks, thus increasing ECC risk (62). Considering the importance of dietary habits (63), it would be more than beneficial to use adequate dietary questionnaire in studies analyzing oral health, as it has been shown that sugar rich diet favours cariogenic potential of human breast milk (43).

Although oral hygiene has one of the most important roles in maintaining oral health, less than one third (28%) of investigated papers addressed frequency of tooth brushing, use of fluorides, duration of brushing and who is brushing child's teeth (18).

Prevention of ECC

Both dental care professionals and paediatricians should have evidence-based knowledge regarding guidelines and potential health risks and be able to provide an adequate and clear information to nursing mothers. We recommend adhering to current paediatric guidelines which promote unrestricted breastfeeding until it is desired by both mother and child.

However, prevention and timely treatment of ECC must also be addressed. There is a need for better education of parents and health care providers about the risk factors, identification of initial lesions and consequences of early childhood caries. Oral health recommendations include avoiding free sugars when introducing solid foods to infant and using fluoridated toothpaste (at least 1000 ppm) and soft toothbrush twice daily, as well as timely consultation with oral health professional (64-66). It is important to inform dental professionals about the importance of breastfeeding and to update their knowledge to enable them to take active role in encouraging breastfeeding in mothers. Taken together, oral and general health care providers should establish a consensus regarding information for parents regarding breastfeeding and prevention of early childhood caries.

Conclusion

Based on presented currently available data, the association between breastfeeding and ECC is contradictory, complex and contains many confounding variables. Taken together, oral and general health care providers should establish a consensus regarding information for parents regarding breastfeeding and prevention of early childhood caries. Further research in this field is needed, especially meta-analyses.

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References

1. Breasfeeding Initiatives: American Academy of Pediatrics; 2013 [Available from: http://www2.aap.org/breastfeeding/sectionOnBreastfeeding.html.
2. Child health - breastfeeding: World Health Organization; 2013 [Available from: http://www.who.int/maternal_child_adolescent/topics/child/nutrition/breastfeeding/en/index.html
3. Salone LR, Vann WF, Jr., Dee DL. Breastfeeding: an overview of oral and general health benefits. J Am Dent Assoc 2013; 144(2):143-51.
4. Michaels KB, Willett WC, Graubard BI, Vaidya RL, Cantwell MM, Sansbury LB, et al. A longitudinal study of infant feeding and obesity through life course. Int J Obes 2007; 31:1078-85.
5. Kramer M, Kakuma R. Optimal duration of

exclusive breastfeeding (Review). Cochrane Database Syst Rev 2002; (1):CD003517.
6. Petrou SP. Incontinent ileovesicostomy in the management of neurogenic bladder dysfunction. Int Braz J Urol 2003;29(2):185-6.
7. Matijevic D, Mladenovic Rankovic S, Kotevic A. Responsive feeding. Zdravstvena zaštita (Health Care) 2018; 1:2-11.
8. Policy on Early Childhood Caries (ECC): Classifications, Consequences, and Preventive Strategies. Pediatr Dent 2017; 39(6):59-61.
9. Policy on Dietary Recommendations for Infants, Children, and Adolescents. Pediatr Dent 2017; 39(6):64-6.
10. Policy on Early Childhood Caries (ECC): Unique Challenges and Treatment Options. Pediatr Dent 2017; 39(6):62-3.
11. Kuhnisch J, Ekstrand KR, Pretty I, Twetman S, van Loveren C, Gizani S, Spyridonos Loizidou M. Best clinical practice guidance for management of early caries lesions in children and young adults: an EAPD policy document. Eur Arch Paediatr Dent 2016; 17(1):3-12.
12. Tinanoff N, Baez RJ, Diaz Guillory C, Donly KJ, Feldens CA, McGrath C, et al. Early childhood caries epidemiology, aetiology, risk assessment, societal burden, management, education, and policy: Global perspective. Int J Paediatr Den 2019; 29(3):238-48.
13. Folayan MO, Sowole CA, Kola-Jebutu A, Owotade FJ. Risk factors for rampant caries in children from southwestern Nigeria. Afr J Med Med Sci 2012; 41(3):249-55.
14. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859):2163-96.
15. El Tantawi M, Folayan MO, Mehaina M, Vukovic A, Castillo JL, Gaffar BO, et al. Prevalence and Data Availability of Early Childhood Caries in 193 United Nations Countries, 2007-2017. Am J Public Health 2018; 108(8):1066-72.
16. Carevic M, Vulovic M, Sindolic M. Integrated Approach in Combating Early Childhood Caries. Balk J Stom 2009; 13:15-20.
17. Milenkovic A, Markovic D, Zdravkovic D, Peric T, Milenkovic T, Vukovic R. Adrenal crisis provoked by dental infection: case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110(3):325-9.
18. Valaitis R, Hesch R, Passarelli C, Sheehan D, Sinton J. A systematic review of the relationship between breastfeeding and early childhood caries. Can J Public Health 2000; 91(6):411-7.
19. Matee MI, Mikx FH, Maselle SY, Van Palenstein Helderman WH. Mutans streptococci and lactobacilli in breast-fed children with rampant caries. Caries Res 1992; 26(3):183-7.
20. Peres RC, Coppi LC, Volpato MC, Groppo FC, Cury JA, Rosalen PL. Cariogenic potential of cows', human and infant formula milks and effect of fluoride supplementation. Br J Nutr 2009; 101(3):376-82.
21. Bowen WH, Lawrence RA. Comparison of the cariogenicity of cola, honey, cow milk, human milk, and sucrose. Pediatrics 2005; 116(4):921-6.
22. Prabhakar AR, Kurthukoti AJ, Gupta P. Cariogenicity and acidogenicity of human milk, plain and sweetened bovine milk: an in vitro study. J Clin Pediatr Dent 2010; 34(3):239-47.
23. Thomson ME, Thomson CW, Chandler NP. In vitro and intra-oral investigations into the cariogenic potential of human milk. Caries Res 1996; 30(6):434-8.
24. Azevedo TD, Bezerra AC, de Toledo OA. Feeding habits and severe early childhood caries in Brazilian preschool children. Pediatr Dent 2005; 27(1):28-33.
25. Aida J, Ando Y, Oosaka M, Niimi K, Morita M. Contributions of social context to inequality in dental caries: a multilevel analysis of Japanese 3-year-old children. Community Dent Oral Epidemiol 2008; 36(2):149-56.
26. Sakuma S, Nakamura M, Miyazaki H. Predictors of dental caries development in 1.5-year-old high-risk children in the Japanese public health service. J Public Health Dent 2007; 67(1):14-9.
27. Tanaka K, Miyake Y. Association between breastfeeding and dental caries in Japanese children. J Epidemiol 2012; 22(1):72-7.
28. Zhou Y, Lin HC, Lo EC, Wong MC. Risk indicators for early childhood caries in 2-year-old children in southern China. Aust Dent J 2011; 56(1):33-9.
29. Campus G, Solinas G, Strohmenger L, Cagetti MG, Senna A, Minelli L, et al. National pathfinder survey on children's oral health in Italy: pattern and severity of caries disease in 4-year-olds. Caries Res 2009; 43(2):155-62.
30. Folayan MO, Sowole CA, Owotade FJ, Sote E. Impact of infant feeding practices on caries experience of preschool children. J Clin Pediatr Dent 2010; 34(4):297-301.
31. Hallett KB, O'Rourke PK. Early childhood caries and infant feeding practice. Community

Dent Health 2002; 19(4):237-42.
32. Jigjid B, Ueno M, Shinada K, Kawaguchi Y. Early childhood caries and related risk factors in Mongolian children. Community Dent Health 2009; 26(2):121-8.
33. Chaffee BW, Feldens CA, Vitolo MR. Association of long-duration breastfeeding and dental caries estimated with marginal structural models. Ann Epidemiol 2014; 24(6):448-54.
34. Yonezu T, Yotsuya K, Yakushiji M. Characteristics of breast-fed children with nursing caries. Bull Tokyo Dent Coll 2006; 47(4):161-5.
35. van Palenstein Helderman WH, Soe W, van 't Hof MA. Risk factors of early childhood caries in a Southeast Asian population. J Dent Res 2006; 85(1):85-8.
36. Peres KG, Nascimento GG, Peres MA, Mittinty MN, Demarco FF, Santos IS, et al. Impact of Prolonged Breastfeeding on Dental Caries: A Population-Based Birth Cohort Study. Pediatrics 2017; 140(1). pii: e20162943.
37. Jones K. Caution needed over breastfeeding advice. Br Dent J 2018; 225(4):275.
38. Milnes AR. Description and epidemiology of nursing caries. J Public Health Dent 1996; 56(1):38-50.
39. Tinanoff N, Kanellis MJ, Vargas CM. Current understanding of the epidemiology mechanisms, and prevention of dental caries in preschool children. Pediatr Dent 2002; 24(6):543-51.
40. Tham R, Bowatte G, Dharmage SC, Tan DJ, Lau MX, Dai X, et al. Breastfeeding and the risk of dental caries: a systematic review and meta-analysis. Acta Paediatr 2015; 104(467):62-84.
41. Victora CG, Bahl R, Barros AJ, Franca GV, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet 2016;387(10017):475-90.
42. LeBouder E, Rey-Nores JE, Raby AC, Affolter M, Vidal K, Thornton CA, et al. Modulation of neonatal microbial recognition: TLR-mediated innate immune responses are specifically and differentially modulated by human milk. J Immunol 2006; 176(6):3742-52.
43. Erickson PR, Mazhari E. Investigation of the role of human breast milk in caries development. Pediatr Dent 1999; 21(2):86-90.
44. Geddes DT, Kent JC, Mitoulas LR, Hartmann PE. Tongue movement and intra-oral vacuum in breastfeeding infants. Early Hum Dev 2008; 84(7):471-7.
45. Ribeiro NM, Ribeiro MA. Breastfeeding and early childhood caries: a critical review. J Pediatr (Rio J). 2004; 80(5 Suppl):S199-210.
46. Roberts GJ, Cleaton-Jones PE, Fatti LP, Richardson BD, Sinwel RE, Hargreaves JA, et al. Patterns of breast and bottle feeding and their association with dental caries in 1- to 4-year-old South African children. 2. A case control study of children with nursing caries. Community Dent Health 1994; 11(1):38-41.
47. Weerheijm KL, Uyttendaele-Speybrouck BF, Euwe HC, Groen HJ. Prolonged demand breast-feeding and nursing caries. Caries Res 1998; 32(1):46-50.
48. Vignarajah S, Williams GA. Prevalence of dental caries and enamel defects in the primary dentition of Antiguan pre-school children aged 3-4 years including an assessment of their habits. Community Dent Health 1992; 9(4):349-60.
49. Rosenblatt A, Zarzar P. Breast-feeding and early childhood caries: an assessment among Brazilian infants. Int J Paediatr Dent 2004; 14(6):439-45.
50. Hong L, Levy SM, Warren JJ, Broffitt B. Infant breast-feeding and childhood caries: a nine-year study. Pediatr Dent 2014; 36(4):342-7.
51. Kramer MS, Vanilovich I, Matush L, Bogdanovich N, Zhang X, Shishko G, et al. The effect of prolonged and exclusive breast-feeding on dental caries in early school-age children. New evidence from a large randomized trial. Caries Res 2007; 41(6):484-8.
52. Dye BA, Shenkin JD, Ogden CL, Marchall TA, Levy SM, Kanellis MJ. The relationship between healthful eating practices and dental caries in children aged 2-5 years in the United States, 1988-1994. Journal of American Dental Association 2004; 135:55-66.
53. Iida H, Auinger P, Billings RJ, Weitzman M. Association between infant breastfeeding and early childhood caries in the United States. Pediatrics 2007; 120(4):e944-52.
54. Nunes AMM, Alves CMC, Araujo FB, Ortiz TML, Ribeiro MRC, Silva AAM, et al. Association between prolonged breast-feeding and early childhood caries: a hierarchical approach. Community Dent Oral Epidemiol 2012; 40:542-9.
55. Moynihan P, Tanner LM, Holmes RD, Hillier-Brown F, Mashayekhi A, Kelly SAM, et al. Systematic Review of Evidence Pertaining to Factors That Modify Risk of Early Childhood Caries. JDR Clin Trans Res 2019; 4(3):202-16.
56. Fontana M. The Clinical, Environmental, and Behavioral Factors That Foster Early

Childhood Caries: Evidence for Caries Risk Assessment. Pediatr Dent 2015; 37(3):217-25.
57. Iwinski S, Gotsch G. Feeding On Cue. New Beginnings 2003; 20(4):126.
58. Vanore JV, Christensen JC, Kravitz SR, Schuberth JM, Thomas JL, Weil LS, et al. Diagnosis and treatment of first metatarsophalangeal joint disorders. Section 2: Hallux rigidus. J Foot Ankle Surg 2003; 42(3):124-36.
59. Derkson GD, Ponti P. Nursing bottle syndrome; prevalence and etiology in a non-fluoridated city. J Can Dent Assoc 1982; 48(6):389-93.
60. Williams SA, Hargreaves JA. An inquiry into the effects of health related behaviour on dental health among young Asian children resident in a fluoridated city in Canada. Community Dent Health 1990; 7:413-20.
61. Harmon Jones C. Duration, Intensity, and Exclusivity of Breastfeeding: Recent Research Confirms the Importance of these Variables. Breastfeeding Abstracts 2006; 25(3):17-20.
62. Hallonsten AL, Wendt LK, Mejare I, Birkhed D, Hakansson C, Lindvall AM, et al. Dental caries and prolonged breast-feeding in 18-month-old Swedish children. Int J Paediatr Dent 1995; 5(3):149-55.
63. Garcia R, Borrelli B, Dhar V, Douglass J, Gomez FR, Hieftje K, et al. Progress in Early Childhood Caries and Opportunities in Research, Policy, and Clinical Management. Pediatr Dent 2015; 37(3):294-9.
64. Peres KG, Chaffee BW, Feldens CA, Flores-Mir C, Moynihan P, Rugg-Gunn A. Breastfeeding and Oral Health: Evidence and Methodological Challenges. J Dent Res 2018; 97(3):251-8.
65. Early Childhood Caries: IAPD Bangkok Declaration. Int J Paediatr Dent 2019; 29(3):384-6.
66. Branger B, Camelot F, Droz D, Houbiers B, Marchalot A, Bruel H, et al. Breastfeeding and early childhood caries. Review of the literature, recommendations, and prevention. Arch Pediatr 2019; 26(8):497-503.

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IMPLEMENTACIJA ARTEFICIJALNIH NEURONSKIH MREŽA I NEURORAČUNARA U MEDICINI: OD FANTASTIČNE IDEJE DO INTELIGENTNIH SKRINING SISTEMA

IMPLEMENTATION OF ARTIFICIAL NEURAL NETWORKS AND NEUROCOMPUTERS IN MEDICINE: FROM FANTASTIC IDEA TO INTELLIGENT SCREENING SYSTEMS

Dejan Živanović[1], Jovan Javorac[1,2], Tijana Javorac[3], Maja Kralj[3]

SAŽETAK

Arteficijalna, informatička neuronska mreža je jedan od razvijenih oblika implementacije sistema veštačke inteligencije u različite oblasti ljudske delatnosti, pa samim tim i u medicinu, gde se pre svega koristi u cilju minimalizacije mogućnosti nastanka profesionalne greške i poboljšanja kvalitativne i prediktivne analize kompleksnih medicinskih i kliničkih podataka. Iako dočekana sa skepsom, primena sistema arteficijalne inteligencije u medicini je za kratko vreme dovela do značajnog podizanja nivoa kvaliteta ostvarene zdravstvene zaštite, a kasnije i stvaranja mogućnosti za implementaciju velikog broja algoritamskih modela za ranu dijagnostiku i skrining velikog broja malignih i hroničnih nezaraznih bolesti. Primena arteficijalnih inteligentnih dijagnostičkih sistema u Srbiji još uvek nije dovoljno zastupljena, a na neophodnost njihove brze implementacije u cilju osavremenjivanja postojeće prakse ukazuju mnogobrojna istraživanja koja potvrđuju uspešnost njihove primene, naročito u oblasti preventivne medicine, ali i brojnih kliničkih disciplina.

Ključne reči: arteficijalna neuronska mreža, neuroračunari, medicina

SUMMARY

Artificial, informatical neural network is one of the developed forms of implementation of the artificial intelligence systems in various fields of human activity, and therefore in medicine, where it is primarily used in order to minimize the possibility of professional error and improve the qualitative and predictive analysis of complex medical and clinical data. Although welcomed with skepticism, the application of artificial intelligence systems in medicine in a short time led to a significant increase in quality of established health care, and later to the creation of opportunities for implementation of a large number of algorithmic models for early diagnosis and screening of a large number of malignant and chronic non-communicable diseases. The usage of artificially intelligent diagnostic systems in Serbia is not yet sufficiently represented, and the necessity of their rapid implementation in order to modernize the existing practice is indicated by numerous researches confirming the success of their application, especially in the field of preventive medicine, as well as in many clinical and scientific disciplines.

Keywords: artificial neural network, neurocomputers, medicine

Uvod

Neuroračunari predstavljaju šestu generaciju kompjutera koji pomoću nanotehnologije sa uspehom simultano obrađuju izuzetno veliki broj informacija dobijenih istovremenim korišćenjem više od hiljadu procesora u cilju memorisanja i obrade podataka zbog čega, suštinski, imitiraju rad ljudskog mozga (1). Informatičku osnovu za rad neuroračunara čini arteficijalna, informatička neuronska mreža (eng. *Artificial Neural Networks*, ANN), jedan

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od razvijenih oblika implementacije sistema veštačke inteligencije koji u osnovi predstavlja sistem konstruisan od određenog broja međusobno povezanih procesnih elemenata, tzv. arteficijalnih neurona (1,2). Svaki od ovih „neurona" ima lokalnu memoriju u kojoj ostaju zabeleženi obrađeni lokalni podaci, ali i oni koji su primljeni putem nekog od spoljašnjih kanala, odnosno veza. Informacije koje se ovim kanalima razmenjuju su obično numeričke prirode, mada je razvoj nanotehnologije u poslednjoj deceniji omogućio i prenošenje drugih vrsta podataka putem neuronskih informatičkih mreža, naročito u situacijama kada nisu poznata pravila koja bi omogućila dovođenje u vezu ulaznih i izlaznih podatka iz željenog sistema. Upravo zbog te činjenice, veštačke neuronske mreže se ne programiraju, već treniraju sposobnost generalizacije unetih primera u određenom vremenskom periodu, i to neposredno pre nego što započne njihova praktična primena (3). Obradom i matematičkim približavanjem različitih nizova algoritama prilikom procesa treninga, dobija se model neuronske mreže sa željenim karakteristikama koje će u kasnijem periodu biti ključne za njenu dalju eksplataciju (1).

Isprva namenjeni prvenstveno za primenu u informatici, matematici i sličnim kognitivnim naukama, neuroračunari se danas sa velikim uspehom koriste u mnogim oblastima ljudske delatnosti. U poslednje tri decenije, široka primena arteficijalne neuroinformatičke tehnologije je evidentna i u eksperimentalnoj i kliničkoj medicini, pre svega u oblasti dijagnostike (4). Osnovni razlog za sve masovniju upotrebu arteficijalnih neuronskih mreža u biomedicinskim naukama je činjenica da ovaj oblik veštačke inteligencije u velikoj meri pojednostavljuje, sistematizuje i automatizuje intelektualne zadatke, čime sve više dobija na značaju u različitim sferama humane intelektualne aktivnosti, pa samim tim i u medicinskim naukama.

Istorija razvoja i počeci implementacije arteficijalnih inteligentnih sistema u medicini

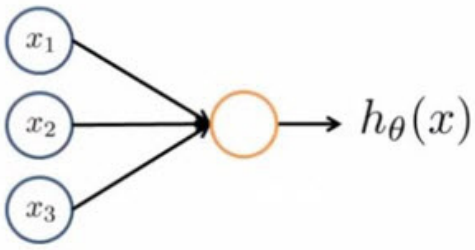
Početak neuroračunarstva se u literaturi najčešće vezuje za 1943.godinu kada je objavljen, do trenutka pisanja ovog rada, čak 16.740 puta citiran članak „*Logički račun ideja svojstvenih nervnoj aktivnosti*" (originalni naslov: „*A logical calculus of the ideas immanent in nervous activity*"), autora *McCullough*-a i *Pitts*-a (5). Iako su u prvom trenutku etiketirana kao naučnofantastična ideja, istraživanja u oblasti informatike zasnovana na radu ljudskog mozga sve češće postaju interesna sfera mnogih naučnika od 50-ih godina 20. veka. Međutim, najveći uticaj na tok istraživanja u ovoj oblasti i dalji razvoj arteficijalnih neuronskih mreža je imao Marvin Minsky, američki matematičar koji je 1951. godine konstruisao prvi, istina primitivni neuroračunar, pod imenom „*Snark*". Odobravanje i priznanje naučne javnosti koje je *Minsky* tada postigao, inspirišu i ohrabruju *Rosenblatt*-a i *Whiteman*-a da 1958. godine razviju neuroračunarski sistem „*Mark I perceptron*", koji je konačno predstavljao prvi neuroračunar sa mogućnošću praktične primene (3). Za razliku od savremenih neuroračunarskih sistema koji se značajno razlikuju od tradicionalnih računara prvenstveno po mogućnosti istovremenog procesiranja velikog broja informacija u cilju rešavanja zadatog zadatka, prvi neuroračunar se u praktičnom smislu nije mnogo razlikovao od tadašnjih računara. Evidentna razlika u odnosu na tadašnje „obične" računare je bila prvenstveno u činjenici korišćenja jednoslojne arteficijalne neuronske mreže, zbog čega je prvi neuroračunar imao izvesnu prednost uspešnog obavljanja određenih funkcija, poput podešavanja težinskih koeficijenata, ali ipak sa ograničenim mogućnostima njihove praktične primene (6). Američka vojna agencija DARPA (eng. *Defense Advanced Research Projects Agency* - Agencija za napredne odbrambene istraživačke projekte) od 1980. godine i zvanično postaje zainteresovana za razvoj tehnologije arteficijalnih neuronskih mreža, usled čega započinje finansiranje neuroinformatičkih istraživanja od strane vlade Sjedinjenih Američkih Država (SAD). Razvoj arteficijalnih neuronskih mreža i neuroračunara počinje u ovom periodu da se odvija ubrzanim tokom, a veliki doprinos njihovoj popularizaciji daje poznati američki fizičar *John Hopfield* (4). Konačno, teorija neuronskih mreža i neuroinformatika se uvode kao predmet na nekoliko elitnih univerziteta u SAD, što predstavlja početak savremene primene arteficijalnih neuronskih mreža u različitim naučnim oblastima.

Objektivno velike mogućnosti precizne i sveobuhvatne prediktivne analize svih raspoloživih medicinskih podataka o bolesniku su dovele do šire upotrebe arteficijalnih neuronskih mreža u medicini u drugoj polovini 20. veka, a kao uspešan početak njihove zvanične primene u medicinskoj praksi se navodi čuveni *Streptomycin system*, razvijen početkom 70-ih godina na Univerzitetu

Stanford u SAD, a u cilju pravovremene i efikasne dijagnoze septičnog šoka. Ovaj informatički sistem se i danas smatra pravim trijumfom neuroračunarske tehnologije, budući da je omogućio ranu detekciju sepse sa preciznošću od 100% (7). U relativno kratkom vremenskom periodu, upotreba različitih sistema zasnovanih na upotrebi veštačkih neuronskih mreža je omogućila pružanje jeftinije, ali istovremeno kvalitetnije i efikasnije zdravstvene zaštite, stvarajući uslove za praktičnu implementaciju velikog broja nelinearnih algoritamskih modela za ranu dijagnostiku malignih i hroničnih nezaraznih bolesti.

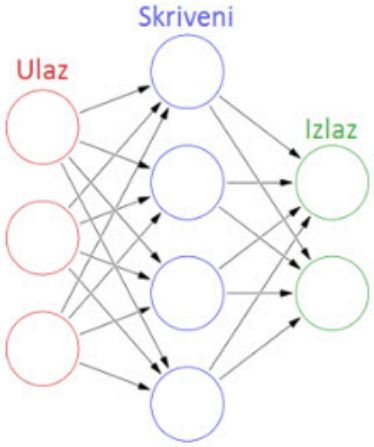
Osnovi građe arteficijalnog neurona i arhitektura neuronske mreže

Poput bioloških, i arteficijalni neuroni su u suštini jednostavne strukture i imaju mogućnost obavljanja određenih funkcija koje imitiraju slične funkcije bioloških neurona. U dostupnoj naučnoj i stručnoj literaturi, uobičajeno da se telo arteficijalnog neurona naziva čvorili, jednostavnije, jedinica (slika 1) (1-4).



Slika 1. Model neurona u arteficijalnim neuronskim mrežama (Perceptron) (8) / *Figure 1. Model of neurons in artificial neural networks (Perceptron) (8)*

Upotrebom arteficijalnih neuronskih mreža mogu se uspešno klasifikovati i rešiti različite vrste informatičkih problema. U praksi, primena neuroinformatičkih tehnologija se pokazala naročito uspešnom u modelovanju sistema kod kojih se ne može jasno odrediti algoritamsko rešenje, naročito onih u kojima su prisutni fizički procesi izuzetno kompleksni ili nedovoljno jasni (9). Pored poznate i jedinstvene sposobnosti da „uče", veštačke neuronske mreže istovremeno pokazuju i visok stepen tolerancije i prilagodljivosti prisustvu različitih poremećaja u ulaznim podacima, što ujedno čini i osnovnu prednost upotrebe neuroračunara u odnosu na konvencionalne informatičke tehnologije prilikom rešavanja problema za koje ne postoji algoritamsko rešenje, ili je ono isuviše komplikovano da bi moglo da bude prepoznato (slika 2) (3).



Slika 2. Model arteficijalne neuronske mreže (8) / *Figure 2. Model of artificial neural networks (Perceptron) (8)*

Arteficijalnu neuronsku mrežu čini niz elemenata: arhitektura (topologija) mreže, odnosno specifična shema uređenja i povezivanja arteficijalnih neurona, zatim prenosna funkcija neurona i zakoni učenja (2,9). U osnovi, arteficijalne neuronske mreže se i razlikuju prema broju neuronskih slojeva. Prvi neuronski sloj je uvek označen kao ulazni, poslednji je izlazni, dok su ostali obično označeni kao skriveni neuronski slojevi. Jedna od najčešćih arhitektura neuronskih mreža je mreža sa tri sloja. Složenije, višeslojne neuronske mreže koje su danas u upotrebi i predstavljaju informatičku osnovu savremenih medicinskih neuroračunara, dizajnirane su tako da pomoću dodatnih elemenata mreže (povratna petlja, sistem za menadžment vremenom), već na ulaznom nivou uspešno prepoznaju i odvoje važne informacije i šeme (1,4).

U suštini, proces treninga arteficijalnih neuronskih mreža je usmeren ka postizanju što višeg stepena preciznosti mreže u kasnijoj eksploataciji, i zasniva se na „učenju" podataka iz velikog broja primera koji postoje u određenoj oblasti. Proces učenja dovodi do korigovanja sinaptičkih težina u veštačkim neuronima; u momentu kada uzorci koji se predstavljaju mreži prestanu da prouzrokuju promene ovih koeficijenata, smatra se da je trening informatičke neuronske mreže uspešno završen. Informatičari primenjuju najčešće tri vrste efikasnog treninga neuronskih mreža, i to:

1. trening sa supervizijom (eng. *Supervused Training*), prilikom koga se mreži istovremeno

predstavljaju i ulazne i izlazne informacije;
2. obučavanje mreže koje je zasnovano na evaluaciji, tzv. trening sa delimičnom supervizijom (eng. *Semi - Supervised Training*), prilikom koga se nakon izvesnog vremena procesuiranja informacija vrši procena uspešnosti rada mreže, bez prethodnog predstavljanja očekivanih izlaznih informacija;
3. trening bez supervizije, odnosno putem samoorganizacije mreže (eng. *Unsupervised Training*), prilikom koga se mreži predstavljaju isključivo ulazne informacije (3,9).

Implementacija arteficijalnih neuronskih mreža u savremene dijagnostičke sisteme

Iako u sistemu zdravstvene zaštite cirkuliše zaista ogroman broj podataka i informacija o korisnicima zdravstvenih usluga, objektivno nije moguće da lekari i drugi zdravstveni radnici sve dobijene podatke jednostavno zapamte i racionalno iskoriste kao pomoć pri efikasnom postavljanju dijagnoza i donošenju odluka o lečenju i planu zdravstvene nege.Takođe, nije redak slučaj da neke informacije ostanu pritajene u hrpi podataka, a važne uzročno-posledične relacije između postojećih podataka o pacijentu usled toga ostanu neotkrivene (10). Teško je i zamisliti kako bi lekar mogao da postavi dijagnozu bolesti za koju nikad nije čuo, medicinska sestra uradi analizu ili test za koji nije znala da postoji, ili da primene savremenu medikamentoznu terapiju koju tokom rada ranije nisu primenjivali. Informatičke neuronske mreže su u svim tim slučajevima od ogromne pomoći, jer se jedna od najvećih prepreka za ostvarivanje efikasne zdravstvene zaštite u savremenim zdravstvenim sistemima danas jednostavno prevazilazi korišćenjem neuroračunara koji mogu da pruže sveobuhvatne i prioritetno determinisane informacije o bolesniku, uvek u odgovarajuće vreme, i uvek na pravom mestu i na pravi način. Različite studije o primeni informatičke neuronske mreže u medicini pokazuju da se sve veći broj problema u sferi zdravstvene zaštite može previzići njihovim korišćenjem, pre svega zbog činjenice da neuroračunari mogu da odrede korelacije tek unetih podataka na osnovu prethodnog znanja (11-14). Čak i u slučaju unosa nepreciznih podataka, arteficijalna neuronskih mreža je u mogućnosti da dođe do željenih izlaza ili bar podataka koji su najbliži željenom izlazu, odnosno sveobuhvatnom rešenju postojećeg problema. Pa ipak, i pored svih prednosti koje pruža upotreba arteficijalnih neuronskih mreža u medicini, svakako ne treba zaboraviti i njihovu osnovnu "manu", odnosno činjenicu da stepen njihove efikasnosti u osnovi zavisi isključivo od efikasnosti primenjenog načina treninga, budući da neuronske mreže nisu u mogućnosti da samostalno kreiraju bilo koju informaciju koja nije prethodno sadržana u trening podacima.

Primena neuroračunara u zdravstvenom sistemu Srbije je još uvek u povoju, a na neophodnost njihove brze implementacije u cilju osavremenjivanja postojeće prakse ukazuju mnogobrojna istraživanja koja potvrđuju uspešnost njihove kliničke i prognostičke (skrining) primene, naročito u oblasti radiologije, kardiologije, urologije, laboratorijske medicine i zdravstvene nege (10,15-17). Primera radi, u zdravstvenim ustanovama razvijenih sistema zdravstvene zaštite, poput sistema u SAD i većini zemalja zapadne Evrope, već niz godina je u upotrebi inteligentni informatički sistem koji sa tačnošću od 89% dijagnostikuje anginu pektoris pomoću primene veštačkih neuronskih mreža (18,19). Takođe, u upotrebi je i sistem neuronskih mreža koji sa 87% tačnosti predviđa maligne bolesti pluća, ali i dijagnostički sistem za predviđanje mogućnosti nastanka fatalne hipoglikemije kod pacijenata sa dijabetesom (20,21). Osim toga, mnoge zdravstvene ustanove u svetu koriste arteficijalnu inteligenciju zasnovanu na algoritmima visoke specifičnosti i senzitivnosti za ranu detekciju karcinoma dojke i skrining drugih vrsta malignoma, dok se jedan od najuspešnijih modela veštačke neuronske mreže koristi za predikciju akutnog glomerulonefritisa, sa tačnošću od čak 99% (10,22,23). U literaturi se takođe može naći podatak da su Dilip Roy Chowdhury i saradnici veoma uspešno primenili "*Back propagation*"neuronsku mrežu za predviđanje i dijagnostikovanje neonatalne bolesti, sa tačnošću predloženog modela od 75% i visokim stepenom stabilnosti razvijenog skrining sistema (24).

Kao i u drugim granama medicine, arteficijalni inteligentni sistemi su i u savremenoj kardiologiji već dugi niz godina postali rasprostranjeno pomoćno sredstvo za ranu dijagnozu i skrining srčanih oboljenja, sa različitim stepenom pouzdanosti u zavisnosti od generacije algoritamskih modela koji su u upotrebi (25,26). Uzimajući u obzir stopu kardiovaskularnog morbiditeta i mortaliteta, dijagnostika bolesti srca je jedno od najvažnijih pitanja savremene preventivne i kliničke

medicine, pa je to i osnovni razlog zbog kojeg istraživači širom sveta godinama pokušavaju da razviju pouzdan inteligentni sistem za podršku u odlučivanju i dijagnostici kod obolelih od akutne koronarne bolesti i drugih oboljenja srčanog mišića. Arteficijalne neuronske mreže su do sada uspešno primenjene za rešavanje problema u dijagnostici i terapiji koronarne arterijske bolesti i infarkta miokarda, u interpretaciji elektrokardiografskog nalaza i otkrivanju aritmija, kao i za sistematičnu analizu u radiografiji i ultrasonografiji srca, ali i koronarografskih snimaka dobijenih primenom perkutane koronarne intervencije (PCI). Satim ciljem je razvijen višeslojni arteficijalni sistem "*Perceptron*", dijagnostički model koji osim tradicionalnih kliničkih, laboratorijskih i funkcionalnih testova, efikasno upotrebljava i druge dostupne podatke o pacijentima (npr. genetske karakteristike obolelih) (27). "*Perceptron*" je arteficijalni inteligentni sistem koji je u prošlosti često tehnički usavršavan, pa tačnost predikcije pojedinih parametara upotrebom ovog sistema iznosi od 64 do čak 94%, u zavisnosti od promene broja ulaznih podataka i broja arteficijalnih neurona (18,28-30).

I na kraju, svakako treba pomenuti da su neuroračunari pronašli svoje mesto i u savremenoj farmaceutskoj industriji za koju su razvijeni inteligentni analitički sistemi koji sa visokom preciznošću mogu izvršiti čitav niz složenih zadataka u procesu proizvodnje i testiranja fizičko-hemijskih osobina farmaceutskih preparata, proučavanju farmakokinetike različitih farmaceutskih formulacija i, konačno, otkrivanju novih lekova (31,32). Primena savremenih neuroinformatičkih sistema omogućava dostupnost prediktornih informacija o ponašanju i svojstvima različitih molekula u budućnosti (33), što svakako ukazuje na još jednu vrstu indirektnog, ali ne i manje značajnog uticaja razvoja arteficijalnih neuronskih mreža na trendove u medicinskoj praksi.

Zaključak

Neuroračunari predstavljaju inteligentne informatičke sisteme koji su još uvek u fazi razvoja i istraživanja, a zasnovani su na primeni jednoslojnih ili višeslojnih arteficijalnih neuronskih mreža – matematičkih, odnosno algoritamskih modela koji, za razliku od tradicionalnih računara, imaju strukturu i operabilnost koji podsećaju na osobine ljudskog mozga. Poslednjih nekoliko decenija je sve evidentnija primena arteficijalnih neuralnih mreža u medicini, a o aktuelnosti ove teme svedoči i činjenica da je u elektronskim bazama podataka trenutno dostupno više od osam hiljada publikacija iz ove oblasti, od kojih je oko hiljadu radova objavljeno u poslednjih godinu dana. Na globalnom nivou, inteligentni računarski sistemi se sve više koriste u sistemu zdravstvene zaštite radi pojednostavljenja procesa rada, bržeg postavljanja dijagnoze u ranom stadijumu bolesti, pouzdane predikcije različitih oboljenja i efikasnijeg planiranja zdravstvene nege, ali ono što je suštinski važno kod primene neuroračunara je činjenica da oni u krajnjem ishodu značajno povećavaju kvalitet ostvarenih zdravstvenih usluga, posebno u preventivnoj medicini. Sa druge strane, iskustvo u kliničkom radu nam pokazuje da postoje različite vrste objektivnih poteškoća zbog kojih postoji realna potreba da se razvije ekspertski sistem za pružanje pomoći u postupku postavljanja medicinske dijagnoze i planiranja lečenja i nege obolelih. Analizirajući rad kliničara, istraživači su u mnogim studijama o korisnosti primene neuroračunara u medicini došli do jedinstvenog zaključka, a to je da ljudi, pa samim tim i zdravstveni radnici, ne mogu analizirati kompleksne podatke bez grešaka. Kako u medicinskoj praksi profesionalna greška veoma često predstavlja ozbiljan problem koji može direktno uticati na tok bolesti pacijenta i ishod lečenja, razvoj sistema veštačkih neuronskih mreža za primenu u zdravstvu dobija sve veći naučni i praktični značaj, i postaje jedno od primarnih oblasti proučavanja u biomedicinskoj informatici.

Literatura

1. Milosavljević M. Veštačka inteligencija. Beograd: Univerzitet „Singidunum", 2015.
2. Marinković J, Simić S, Božović Z, Dačić M, Kocev N. Mali rečnik informatike u medicini [monograph on the Internet]. Beograd: Institut za socijalnu medicinu, statistiku i istraživanja u zdravstvu, 1995 [cited 2018 Dec 24]. Available at: http://www.mfub.edu.rs/dotAsset/38234.pdf/.
3. Dačić M. Biomedicinska naučna informatika. 3. izd. Beograd: Naučna knjiga; 2006.
4. Marinković J, Babić D, Maksimović R, Stanisavljević D. Elementi računarske podrške u naučnim istraživanjima iz oblasti medicine. Srp Arh Celok Lek 1995; 123 Suppl 2:14-7.

5. Warren S, McCulloch WP. A logical calculus of the ideas immanent in nervous activity. Bull Math Biophys 1943;5(4):115-33.
6. Yadav N, Yadav A, Kumar M. History of neural networks. In: An introduction to neural network methods for differential equations. Dordrecht: Springer, 2015: pp. 13-5.
7. Xhumari E, Manika P. Application of artificial neural networks in medicine. In: RTA-CSIT, 2016: pp. 155-7.
8. Gavran S. Veštačke neuronske mreže u istraživanju podataka: pregled i primena [master teza]. Beograd: Univerzitet u Beogradu,Matematički fakultet, 2016.
9. Vilović I, Nađ R, Šipuš Z. Predviđanje rasprostiranja elektromagnetskog polja u bežičnim komunikacijama zatvorenog prostora zasnovano na neuronskim mrežama. Naše more 2008; 55(1):59-68.
10. Amato F, Lopez A, Pena-Mendez EM, Vanhara P, Hampl A, Havel J. Artificial neural networks in medical diagnosis. J Appl Biomed 2013; 11(2):47-58.
11. Al-Shayea QK. Artificial neural networks in medical diagnosis. International Journal of Computer Science Issues 2011; 8(2):150-4.
12. Qayyum A, Anwar SM, Awais M, Majid M. Medical image retrieval using deep convolutional neural network. Neurocomputing 2017; 266:8-20.
13. Moeskops P, Viergever MA, Mendrik AM, de Vries LS, Benders MJ, Išgum I. Automatic segmentation of MR brain images with a convolutional neural network. IEEE transactions on medical imaging 2016; 35(5):1252-61.
14. Annarumma M, Withey SJ, Bakewell RJ, Pesce E, Goh V, Montana G. Automated triaging of adult chest radiographs with deep artificial neural networks. Radiology 2019; 291(1):196-202.
15. Beauchet O, Noublanche F, Simon R, Sekhon H, Chabot J, Levinoff EJ, et al. Falls Risk Prediction for Older Inpatients in Acute Care Medical Wards: Is There an Interest to Combine an Early Nurse Assessment and the Artificial Neural Network Analysis? J Nut Health Aging 2018; 22(1):131-37.
16. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts HJWL. Artificial intelligence in radiology. Nat Rev Cancer 2018; 18:500-10.
17. Dukic I, Ellison J, Moore M, Collin N, Timoney A, Philip J. Predicting the success of extra-corporal shock wave lithotripsy (ESWL) in ureteric stone disease using pre-operative parameters and an artificial neural network. Eur Urol Suppl 2017; 16(7):e2560.
18. Zahar Đorđević M. Klasifikacija srčanih oboljenja pomoću neuronskih mreža [doktorska disertacija]. Kragujevac: Univerzitet u Kragujevcu - Fakultet inženjerskih nauka, 2014.
19. Awang MK, Siraj F. Utilization of an artificial neural network in the prediction of heart disease. International Journal of Bio-Science and Bio-Technology 2013; 5(4):159-65.
20. Ganesan N, Venkatesh K, Rama MA, Malathi Palani A. Application of neural networks in diagnosing cancer disease using demographic data. Int J Comput Appl 2010;1(26):76-85.
21. Chan KY, Ling SH, Dillion TS, Nguyen HT. Diagnosis of hypoglycemic episodes using a neural network based rule discovery system. Expert Syst Appl 2011; 38(8):9799-808.
22. Mehdy MM, Ng PY, Shair EF, Md Saleh NI, Gomes C. Artificial neural networks in image processing for early detection of breast cancer. Computational and Mathematical Methods in Medicine, 2017. Available at: https://doi.org/10.1155/2017/2610628
23. Roffman D, Hart G, Girardi M, Ko CJ, Deng J. Predicting non-melanoma skin cancer via a multi-parameterized artificial neural network. Sci Rep 2018; 8:1701.
24. Chowdhury DR, Chatterjee M, Samanta RK. An artificial neural network model for neonatal disease diagnosis. International Journal of Artificial Intelligence and Expert Systems 2011; 2(3):96-106.
25. Kumaravel N, Sridhar KS, Nithiyanandam N. Automatic diagnosis of heart diseases using neural network. In: Proceedings of the 15th Southern Biomedical Engineering Conference; 1996 Apr 04-06; Washington, USA. New York: IEEE Conference Publications, 1996.
26. Krittanawong C, Zhang H, Wang Z, Aydar M, Kitai T. Artificial intelligence in precision cardiovascular medicine. J Am Coll Cardiol 2017; 69(21):2657-64.
27. Atkov OY, Gorokhova SG, Sboev AG, Generozov EV, Muraseyeva EV, Moroshkina SY, Cherniy NN. Coronary heart disease diagnosis by artificial neural networks including genetic polymorphisms and clinical parameters. J Cardiol 2012; 59(2):190-94.
28. Malan S. Use of ANN for diagnosis of myocardial infarction. In: Lele R, editor. Computers in medicine – Progres in medical informatics. New Delhi: Tata McGraw-Hill Education, 2005: pp. 255-6.
29. Heidari E, Sobati MA, Movahedirad S. Accurate prediction of nanofluid viscosity

using a multilayer perceptron artificial neural network (MLP-ANN). Chemometrics and Intelligent Laboratory Systems 2016; 155:73-85.
30. Kakar A, Sheikh N, Ahmed B, Iqbal S, Rahman A, Kakar SA, et al. Systematic analysis and classification of cardiac rate variability using artificial neural network. International Journal of Advanced Computer Science and Application 2018; 9(11):746-50.
31. Pathak Y, Laghuvarapu S, Mehta S, Priyakumar U. Chemically interpretable graph interaction network for prediction of pharmacokinetic properties of drug-like molecules. ChemRxiv 2019 (Preprint). doi: 10.26434/chemrxiv.10282346.v1
32. Baskin II, Winkler D, Tetko IV. A renaissance of neural networks in drug discovery. Expert Opin Drug Dis 2016; 11(8):785-95.
33. Ekins S. The next era: deep learning in pharmaceutical research. Pharm Res 2016; 33(11):2594-603.

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PREDNOSTI I NEDOSTACI VEGETARIJANSKE ISHRANE

ADVANTAGES AND DISADVANTAGES OF VEGETARIAN NUTRITION

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SAŽETAK

U modernom dobu najvažniji motivi za izbor vegetarijanstva su etički, zdravstveni, ekološki i hedonistički. Takođe, važnu ulogu imaju porodica i kulturološka tradicija. Većina radova ukazuje da se kod vegetarijanaca mnogo ređe javljaju kardiovaskularne i maligne bolesti, kao i dijabetes tip 2, u odnosu na nevegetarijance. Ovim načinom ishrane dolazi do redukcije telesne mase, hipertenzije i nivo LDL - holesterola. Međutim, vegetarijanski način ishrane može biti povezan sa nedovoljnim unošenjem omega-3 polinezasićenih masnih kiselina, proteina, kalcijuma, cinka, gvožđa, vitamina B12 i vitamina D. Zdravstveni radnici moraju poznavati vegetarijanstvo dovoljno dobro kako bi pravilno savetovali pacijente kod izbora ovakvog načina ishrane. U mnogim smernicama za pravilno sprovođenje vegetarijanstva, a naročito veganizma naglašena je potreba za fortifikovanim namirnicama, a ponekad i dijetetskim suplementima. Upravo zbog svega navedenog, cilj ovog rada je bio da se sagledaju prednosti i nedostaci vegetarijanstva.
Ključne reči: vegetarijanstvo, veganizam, zdravlje

SUMMARY

In the modern age, the most important motives for choosing vegetarianism are ethical, health, environmental and hedonistic. Family and cultural tradition also play an important role. Most studies indicate that cardiovascular and malignancies, as well as type 2 diabetes, are much less likely to occur in vegetarians than non-vegetarians. This diet leads to reduction of weight, hypertension and LDL cholesterol levels. However, the vegetarian diet may be associated with an insufficient intake of omega-3 polyunsaturated fatty acids, protein, calcium, zinc, iron, vitamin B12 and vitamin D. Health care professionals need to be familiar with vegetarianism well enough to properly advise patients on their dietary choices. Many guidelines for the proper conduct of vegetarianism, and in particular veganism, emphasize the need for fortified foods and sometimes dietary supplements. Because of all of the above, the aim of this paper was to analyse the advantages and disadvantages of vegetarianism.
Keywords: vegetarian, vegan, health

Uvod

Termin vegetarijanstvo (sastavljen od dve reči latinskog porekla: vegetus - krepak/čio i vegetatio - biljke) datira iz sredine XIX veka (mada se pojavljuje još u VI veku pre nove ere), a osmislilo ga je Udruženje vegetarijanaca kao način ishrane kojim se izbegavaju sve ili pojedine namirnice životinjskog porekla (1). Vegetarijanski način ishrane podrazumeva delimično ili potpuno ne konzumiranje namirnica animalnog porekla. Neradikalni vegetarijanci od namirnica životinjskog porekla najčešće konzumiraju mleko i mlečne proizvode, kao i jaja, a vegani, kao najstroža forma vegetarijanstva, u ishrani isključivo koriste namirnice biljnog porekla (2). Najčešće u ishrani vegetarijanaca dominaraju voće, povrće, integralne žitarice, semenke, orašasti plodovi, pasulj, tofu, itd.

Dosadašnja ispitivanja ukazuju da, pored religijskih razloga, i nereligijski motivi mogu usloviti takvu ishranu: briga zbog okrutnosti prema životinjama, odvratnost prema mesu, običaji, verovanja i uticaj porodice ili autoriteta (3-5). Svest da vegetarijanstvo pomaže očuvanju životne sredine ima psihološku dimenziju (6). Jabs (7) je proučavao kako način života utiče na izbor vegetarijanske ishrane. Interesantno je da zdravstveni vegetarijanci postepeno menjaju način ishrane, obično iz zdravstvenih razloga (npr. gubitka telesne težine), dok su kod etičkih vegetarijanaca promene u načinu ishrani iznenadne/nagle i smatraju se moralnim imperativom (7,8).

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Upravo zbog svega navedenog, cilj ovog rada je bio da se sagledaju prednosti i nedostaci vegetarijanstva.

Vrste vegetarijanstva

Brojna istraživanja ukazuju da postoje različite vrste vegetarijanstva, a najčešće su striktno vegetarijanstvo, sirovo vegetarijanstvo, frutarijanstvo, ovo - vegetarijanstvo, lakto - vegetarijanstvo i pesko-vegetarijanstvo (9). Specifičnosti ovih različitih vrsta vegetarijanstva su opisane u tabeli 1.

Tabela 1. Vrste i karakteristike vegetarijanstva (preuzeto iz reference 8) / *Types and characteristics of vegetarianism (taken from reference 8)*

Vrsta vegetarijanstva / *Types of vegetarianism*	Dozvoljena hrana / *Allowed food*	Hrana koja se ne koristi / Unused food
Striktno vegetarijanstvo / *Strict vegetarianism*	Povrće, riba / *Vegetables, fish*	Jaja, mleko, mlečni proizvodi, med, crni i beli luk, praziluk i druge vrste luka, proizvodi koji mogu sadržati životinjske sastojke koji nisu navedeni na deklaraciji (želatin) ili se koriste u procesu pravljenja hrane (sirište iz stomaka životinje, pravljenje sira itd.)/ *Eggs, milk, dairy products, honey, onions and garlic, leeks and other types of onions, products that may contain animal ingredients not listed on the declaration (gelatin) or used in the process of making food (rennet from the animal, making cheese, etc.)*
Sirovo vegetarijanstvo / *Raw vegetarianism*	Sveže i nekuvano voće, orasi, semenke, povrće / *Fresh and uncooked fruit, nuts, seeds, vegetables*	Jaja, mleko i mlečni proizvodi, med, kuvana hrana / Eggs, milk and dairy products, honey, cooked food
Frutarijanstvo / *Frutarianism*	Sočno voće, orasi, semenke i povrće bez oštećenja biljke pri branju / *Juicy fruits, nuts, seeds and vegetables without damaging the plant when picked*	Jaja, mleko, med, sočno voće, orasi, semenke i ostalo povrće pri čijem branju se oštećuje biljka / Eggs, milk, honey, juicy fruits, nuts, seeds and other vegetables whose picking damages the plant
Lakto-ovo-vegetarijanstvo / *Lacto-ovo-vegetarianism*	Jaja, mleko i mlečni proizvodi / *Eggs, milk and dairy products*	Meso, riba / Meat, fish
Ovo-vegetarijanstvo / *Ovo-vegetarianism*	Jaja / *Eggs*	Mleko i mlečni proizvodi / *Milk and dairy products*
Lakto-vegetarijanstvo / *Lacto-vegetarianism*	Mleko i mlečni proizvodi / *Milk and dairy products*	Meso, riba, jaja, med, proizvodi napravljeni od kože i mast / *Meat, fish, eggs, honey, products made of leather and fat*
Pesko-vegetarijanstvo / *Pesco-vegetarianism*	Riba / *Fish*	Meso, jaja, med, proizvodi napravljeni od kože i mast / *Meat, eggs, honey, products made of leather and fat*

Veganizam

U odnosu na vegetarijanstvo, veganizam je njegova najstroža forma, koja predstavlja filozofiju i način života koji nastoji isključiti (koliko je to praktično moguće) sve oblike iskorištavanja i okrutnosti prema životinjama (10). Drugim rečima životinje ne treba koristiti za ishranu, odeću ili bilo koju drugu svrhu. Osim toga veganizam na ovaj način širi i promoviše upotrebu alternative, a sve u cilju dobrobiti za životinje, ljude i životnu sredinu. U prehrambenom smislu ona označava praksu izostavljanja svih proizvoda koji su u celini ili

delimično životinjskog porekla (10).

Prema nekim autorima, postoje tri osnovne vrste veganizma: konformistički, organizovani i individualistički (11). Konformistički vegani nisu čvrsto uvereni u veganizam i ponekad ga napuštaju zbog nedoslednosti. Međutim, ukoliko ipak postanu još čvršći u svojim uverenjima, prelaze u druge oblike veganizma. Organizovani vegani su duboko uvereni u vegansku ideologiju, a njihove ideje se odlikuju etičkim odnosom prema životinjama, borbom za solidarnost i slobodnije političke stavove. Oni veruju da su ljudi i životinje jednaki, te protestuju protiv mučenja životinja i organizuju javne proteste i debate, kao i kampanje protiv pojedinih kompanija i bojkotuju njihove proizvode. Individualistički vegani su duboko uvereni u vegansku ideologiju, ali nemaju potrebu za ujedinjavanjem i interakcijom sa drugim veganima. Za njih veganizam nije stil života već samo način ishrane, koji ne nameću drugim ljudima.

Zdravstveni i etički vegetarijanci

Motivacija za vegetarijanstvo može biti raznovrsna i nije povezana samo sa stavom o ishrani, već i sa identitetom. Lični motivi za prelazak na vegetarijanstvo mogu biti zdravstveni ili etički (6,8,12).

Zdravstveni vegetarijanci prelaze na ovakav vid ishrane zbog zabrinutosti za svoje zdravlje i u cilju prevencije nastanka pojedinih bolesti i fokusiraju se na poboljšanje sopstvenog zdravstvenog stanja. Brinu i o normalnoj telesnoj masi, što predstavlja i prilagođavanje važećim socijalnim normama zapadne kulture koja promoviše skladnu građu i odlično zdravlje (13). Zdravstveni vegetarijanci uglavnom postepeno izostavljaju meso u ishrani i retko prelaze na veganizam.

Za razliku od zdravstvenih, etički vegetarijanci usvajaju ovakav način ishrane zbog moralnih principa koji uključuju i dobrobit životinja, a neki iz religijskih i kulturnih uverenja. Etički vegetarijanci naglo prelaze na ovakav način ishrane. Konzumiranje mesa za njih predstavlja emocionalni stres i uvereni su da doprinose boljem položaju životinja. Oni smatraju vegetarijanstvo filozofskim problemom (14).

Prednosti vegetarijanstva

Globalno povećanje broja osoba sa kardiovaskularnim i malignim bolestima, dijabetesom i gojaznošću povezano je sa starenjem populacije, ubrzanom neplanskom urbanizacijom i globalnim širenjem nezdravih stilova života, koji uključuju nepravilnu ishranu, smanjenu fizičku aktivnost, pušenje, nezdravo pijenje alkohola, itd. Upravo zbog želje ljudi da smanje rizik od svih navedenih hroničnih nezaraznih bolesti, vegetarijanstvo je, svuda u svetu, steklo sve veću popularnost tokom proteklih decenija (9,14).

U brojnim istraživanjima je uočeno da je smrtnost od hroničnih nezaraznih bolesti, kao što su kardiovaskularne i maligne bolesti i dijabetes tipa 2, značajno manja kod vegetarijanaca nego kod nevegetarijanaca (15-23). Takođe, vegetarijanci imaju manji rizik obolevanja od gojaznosti, hipertenzije, infarkta miokarda, moždanog udara, dijabetesa, artritisa, neurodegenerativnih i malignih bolesti (posebno od kolorektalnog raka i raka prostate) (9,17, 21-23).

Vegetarijanstvo i veganstvo su korisni za povećanje unosa zaštitnih materija (dijetnih vlakana, magnezijuma, folne kiseline, vitamini C i E, gvožđa) i fitohemikalija, kao i za smanjivanje unosa zasićenih masti koje povećavaju učestalost nekih hroničnih bolesti (16,17). Ishrana kod vegetarijanstva i veganizma bogatija je i omega-6 polinezasićenim masnim kiselinama, karotenoidima, flavonoidima, drugim fitohemikalijama i antioksidansima (18-19).

Danas su u mnogim zemljama, posebno u zemljama u razvoju, rasprostranjene visokokalorične namirnice i one su ujedno i jeftinije i šire dostupne u odnosu na niskokalorične namirnice (18). S tim u vezi, semivegetarijanstvo koje podrazumeva manji unos mesa u pokušaju da se kontroliše telesna masa je korisno u prevenciji gojaznosti koja je globalni javno-zdravstveni problem (18).

Kod zdravih osoba, vegetarijanska ili veganska dijeta može obezbediti adekvatne količine svih nutrijenata neophodnih ukoliko su ovakav način ishrane dobro isplanira. Stepen u kome ove dijete mogu imati korisne efekte zavisi od dužine njihovog sprovođenja, pola, pušačkog statusa, konzumiranja alkohola, telesne mase, socioekonomskog statusa, fizičke aktivnosti i niza drugih faktora.

Nedostaci vegetarijanstva

Meso i proizvodi od mesa ne sadrže dijetetska vlakna i fitohemikalije, ali sadrže veliku količinu holesterola i zasićenih masti koje povećavaju nivo koncentracije LDL-holesterola (20). Povećan unos crvenog i prerađenog mesa je povezan sa

kardiovaskularnim i malignim bolestima, kao i sa dijabetes melitusom tipa 2 (20). Pored toga, tokom zagrevanja i pečenja mesa stvaraju se kancerogena jedinjenja, kao što su aromatični ugljovodonici i heterociklični amini.

Međutim, vegetarijanstvo i veganstvo podrazumevaju, pored manjeg unosa ukupnih masti i nedovoljan unos omega-3 polinezasićene masnih kiselina, kalcijuma, joda, cinka, dvovalentnog gvožđa, vitamina B12 i D (24). Pored toga, neke studije su potvrdile da neuhranjenost i slabija razvijenost dece, pa čak i smrtni slučajevi, mogu da se povežu sa veganstvom tako da ono generalno nije preporučljivo za decu (25-27). Neki autori su uočili da rast i razvoj dece vegana može biti u normalnom opsegu (28), dok drugi da deca vegani imaju usporen rast, koji mogu nadoknaditi do desete godine života (29).

U nekoliko studija je analizirana povezanost vegetarijanstva i veganstva sa pojedinačnim bolestima. U nekim ranije sprovedenim studijama otkriveno je da vegetarijanci imaju veću gustinu kostiju u odnosu na osobe koje jedu meso (30-32), dok u kasnije sprovedenim studijama ova veza nije bila potvrđena (33-34). Dyett i saradnici, takođe, ukazuje na moguću povezanost između vegetarijanstva, niske gustine kostiju, nižeg unosa kalcijuma i razvoja osteoporoze (35).

Vegetarijanstvo u cilju smanjenja telesne mase može se povezati sa poremećajem ponašanja (36,37). U nekim, mada ne svim studijama, uočeno je da se mentalna anoreksija češće javlja kod vegetarijanaca (36,37). Vegetarijanstvo nije glavni uzrok poremećaja ponašanja u ishrani, ali najverovatnije pomaže održavanju ovog poremećaja. Timko i saradnici navode da vegani i vegetarijanci jedu manje obroke, nisu veliki hedonisti i lakše prihvataju različite tipove hrane u odnosu na semivegetarijance (38).

Neki istraživači ukazuju da ovaj način ishrane može može dovesti do anemije, slabljenja vida, umora, slabosti mišića, izraženijih menstruacijskih tegoba i lošije mentalne performanse.

Zaključak

Na osnovu dosadašnjih rezultata istraživanja jasno je da postoje određeni nedostaci u vegetarijanskoj ishrani, ali oni se mogu prevazići pravilnim planiranjem ishrane vegetarijanaca, odnosno potrebno je zameniti nedostajuće namirnice drugim, koje obezbeđuju zadovoljavajuću količinu sličnih hranljivih sastojaka. Takođe, neophodna su dalja istraživanja o prednostima i nedostacima vegetarijanske ishrane, kao i o njenom uticaju na prevenciju obolevanja od različitih hroničnih nezaraznih poremećaja zdravlja.

Literatura

1. Ruby MB. Vegetarianism. A blossoming field of study. Appetite 2012; 58:141–50.
2.Nikolić M (ured). Dijetetika. Niš: Medicinski fakultet Univerziteta u Nišu, WUS, 2008.
3. Rosenfeld DL, Burrow AL. Vegetarian on purpose: Understanding the motivations of plant-based dieters. Appetite 2017; 116:456-463.
4. de Boer J, Schösler H, Aiking H. Towards a reduced meat diet: Mindset and motivation of young vegetarians, low, medium and high meat-eaters. Appetite 2017; 113:387-97.
5. Nikolić M, Jovanović A, Stanković A. Šta pediajtri treba da znaju o veštačkim zaslađivačima? Prev Ped 2019; 5(1-2):7-11.
6. Mathieu S, Dorard G. Vegetarianism and veganism lifestyle: Motivation and psychological dimensions associated with selective diet. Presse Med 2016; 45(9):726-33
7. Jabs J, Devine CM, Sobal J. Model of the process of adopting vegetarian diets Healt vegetarians and ethical vegetarians. J Nutr Educ 1998; 30:196-203.
8. Pilis W, Stec K, Zych M, Pilis A. Health benefits and risk associated with adopting a vegetarian diet. Rocz Panstw Zakl Hig 2014; 65(1):9-14.
9. Petti A, Pulmieri b, Vadala M, Laurino C. Vegetarianism and veganism:not only benefits but also gaps. A review. Progress in Nutr 2017; 19(39):229-42.
10. Craig W J. Health effects of vegan diets. Am J Clin Nutr 2009; 89:1627S–33S.
11. Larsson CL, Rönnlund U, Johansson G, Dahlgren L. Veganism as status passage: the process of becoming a vegan among youths in Sweden. Appetite 2003; 41(1):61-7.
12. Pribis P, Pencak RC, Grajales T. Beliefs and attitudes toward vegetarian lifestyle across generations. Nutrients 2010; 2(5):523-31.
13. Stein RI, Nemero FCJ. Moral overtones of food: Judgement of others based on what they eat. Pers Soc Psychol Bull 1995; 21:480-90.
14. Manohar R, Kessler CS. Āyurveda's Contributions to Vegetarian Nutrition in Medicine. Forsch Komplementmed 2016; 23(2):89-94.
15. Li D. Effect of the vegetarian diet on non-communicable diseases. J Sci Food Agric

2014; 94(2):169-73.
16. Davey GK, Spencer EA, Appleby PN, et al. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. Public Health Nutr 2003; 6(3):259-69.
17. Dewell A, Weidner G, Sumner MD, et al. A very-low-fat vegan diet increases intake of protective dietary factors and decreases intake of pathogenic dietary factors. J Am Diet Assoc 2008; 108(2):347-56.
18. Nikolić M, Miladinović B, Perović M. Voće i povrće kao fundamentalna hrana u primarnoj prevenciji kardiovaskularnih bolesti. Zdravstvena zaštita 2017; 1:47-53
19. Drewnowski A, Darmon N. The economics of obesity Dietary energy density and energy cost. Am J Clin Nutr 2005; 82:S265–73.
20. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. Circulation 2010; 121:2271–83.
21. Djousse´ L, Arnett DK, Coon H, et al. Fruit and vegetable consumption and LDL cholesterol: the National Heart, Lung, and Blood Institute Family Heart Study. Am J Clin Nutr 2004; 79:213–7.
22. Key TJ, Appleby PN, Spencer EA, et al. Cancer incidence in British vegetarians. Br J Cancer 2009; 101:192–7.
23. Yang SY, Li XJ, Zhang W, et al. Chinese lacto-vegetarian diet exerts favorable effects on metabolic parameters, intima-media thickness, and cardiovascular risk in healthy men. Nutr Clin Pract 2012; 27:392–8.
24. Li D. Chemistry behind Vegetarianism. Agric Food Chem 2011; 59(3):777-84.
25. Roberts I, West R, Ogilvy D, et al. Malnutrition in infants receiving cult diets: a form of child abuse. BMJ 1979; 1:296-98.
26. Zmora E, Gorodischer R, Bar-Ziv J. Multiple nutritional deficiencies in infants from a strict vegetarian community. Am J Dis Child 1979;133(2):141-4.
27. Shinwell ED, Gorodischer R. Totally vegetarian diets and infant nutrition. Pediatrics 1982; 70(4):582-6.
28. Sanders T. Ggrowth and development of British vegan children. Am J Clin Nutr 1998; 48:822-25.
29. Sanders T and Manning J. The growth and development of vegan children. J Hum Nutr Dietet 1992;5:11-21
30. Marsh A, Sanchez T, Michelsen O, et al. Vegetarian life-style and bone mineral density. Am J Clin Nutr 1988;48:837–41.
31. Tylavsky F and Anderson J. Bone health of elderly lacto-ovo-vegetarians and omnivorous women. Am J Clin Nutr 1988; 48:842–9.
32. Hunt IF, Murphy NJ, Henderson C, et al. Bone mineral content in postmenopausal women: comparison of omnivores and vegetarians. Am J Clin Nutr 1989; 50:517–23.
33. Lloyd T, Schaeffer J, Walker M, et al. Urinary hormonal concentrations and spinal bone densities of premenopausal vegetarian and omnivorous women. Am J Clin Nutr 1991;56:699–704.
34. Lau E, Kwok T, Woo J, et al. Bone mineral density in Chinese elderly female vegetarians, vegans, lactoovovegetarians and omnivores. Eur J Clin Nutr 1998; 52:60–4.
35. Dyett PA, Sabaté J, Haddad E et al. Vegan lifestyle behaviors An exploration of congruence with health-related beliefs and assessed health indices. Appetite 2013; 67:119-24.
36. Kadambari R, Gowers S, Crisp AH. Some correlates of vegetarianism in anorexia nervosa. Int J Eat Disord 1986; 5:539–44.
37. O' Connor MA, Touyz SW, Dunn SM, et al. Vegetarianism in anorexia nervosa? A review of 116 consecutive cases. Med J Aust 1987; 147(11–12):540–2.
38. Timko A , Hormes JM, Chubski J. Will the real vegetarian please stand up? An investigation of dietary restraint and eating disorder symptoms in vegetarians versus non-vegetarians. Appetite 2012; 58:982–90.

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Acknowledgment

Acknowledgments should be given to all contributors who have contributed to the realization of the work but who haven't met the criteria for authorship, as well as to all those who have financially and materially assisted in the realization of the research.

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