

Uloga izabranog lekara u zaustavljanju progresije dijabetesne nefropatije i retinopatije

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General Physician's role in stalling the progression of diabetic nephropathy and retinopathy

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Sažetak

Uvod. Broj obolelih od dijabetesa raste u svetu i poprima razmere epidemije. Na rano otkrivanje i kontrolu faktora rizika za mikrovaskularne komplikacije mogu značajno da utiču izabrani lekari.

Cilj rada. Utvrditi učestalost dijabetesne nefropatije i retinopatije i mere koje su izabrani lekari preduzeli radi sprečavanja daljeg napredovanja mikrovaskularnih komplikacija, a koje se ne odnose na glikoregulaciju.

Metod. Istraživanje je sprovedeno kao studija preseka u novembru 2017. godine, na uzorku od 100 pacijenata Save-tovališta za šećernu bolest Doma zdravlja Zemun. Podaci su preuzeti iz dijabetoloških kartona stotinu pacijenata koji su pregledani tokom tog meseca. Uzeti su podaci iz protokola zabeleženi pri prvoj poseti, pre intervencije lekara iz Save-tovališta. Podaci su obrađeni deskriptivnom i analitičkom statistikom.

Rezultati. Dijabetesnu nefropatiju imalo je 15% ispitanika, a dijabetesnu retinopatiju 14,5%. Od 100 pacijenata nefrologu je upućeno troje, od toga dvoje sa proteinurijom. Na testiranje za dijabetesnu retinopatiju oftalmologu je upućeno 69 ispitanika, od kojih je 10 imalo retinopatiju. Izabrani lekari su uključili ACEI - inhibitore angiotenzin konvertujućeg enzima ili ARB - blokatore angiotenzinskih receptora kod 73,3% pacijenata sa proteinurijom, odnosno kod 64,7% pacijenata bez proteinurije.

Zaključak. Učestalost dijabetesne nefropatije iznosi 15% a dijabetesne retinopatije 14,5%. Izabrani lekari su uputili na skrining, odnosno testiranje za dijabetesnu retinopatiju 69% ispitanika i uveli ACEI/ARB u terapiju kod više od 73,3% ispitanika sa dijabetesnom nefropatijom. Mali procenat ispitanika upućen je na nefrološku konsultaciju.

Ključne reči: dijabetes, mikrovaskularne komplikacije, skrining, proteinurija.

Abstract

Introduction: The number of diabetic patients is ever increasing worldwide and it reaches epidemic proportions. General physicians (GPs) may have a significant impact on early detection and risk factors control, the issues which may lead to microvascular complications.

Objective: Establish the incidence of diabetic nephropathy and retinopathy and review the measures GPs undertook to stop the further microvascular complications advance (but not the ones related to glucose measurement).

Method: The research was performed as a cross-sectional study in November 2017, on 100 patients in the Counseling center for diabetes, Primary Health care Center, Zemun. Data were taken from the patients' diabetic medical charts and reviewed. They were taken at the patient's first visit, before a physician's intervention. Descriptive and analytical statistics were used for data processing.

Results: Diabetic nephropathy was found in 15% of the participants and retinopathy in 14.5%. Out of 100 participants, 3 were sent to a nephrologist. Out of these 3, 2 had proteinuria. For the sake of retinopathy screening, 69 patients were referred to an ophthalmologist. Among them, retinopathy was found in 10. GPs started ACEIs (angiotensin-converting enzyme inhibitors) and ARBs (angiotensin receptor blockers) in 73.3% of patients with proteinuria and 64.7% without proteinuria.

Conclusions: The incidence of diabetic nephropathy was 15% and diabetic retinopathy 14.5%, in our research. GPs referred 69% of the patients to an ophthalmologist for retinopathy screening and started ACEI/ARB in more than 73.3% of the participants with diabetic nephropathy. Small percent was referred to a nephrologist.

Keywords: diabetes, microvascular complications, screening, proteinuria.

Увод

Savremeni svet je zahvatila epidemija dijabetes melitusa tip 2, koja postaje ozbiljan teret za društvo u celini¹. Prevalencija obolevanja od dijabetesa tip 2 je u stalnom porastu² u svim regionima Evrope. U Srbiji je procenat obolelih od dijabetesa sa 8,6% u 2010. porastao na 13,3% u 2017. godini², pri čemu više od 90% obolelih dijabetičara jesu lica obolela od dijabetesa tip 2³. Procenjuje se da jedna trećina obolelih u trenutku postavljanja dijagnoze već ima neku od komplikacija ove bolesti³. Najveći broj smrtnih ishoda posledica je makrovaskularnih komplikacija dijabetesa, ali se značaj mikrovaskularnih komplikacija ogleda u učešću u ukupnoj invalidnosti osoba obolelih od ove bolesti¹.

Troškovi lečenja hronične bubrežne insuficijencije (HBB) u periodu 2006.-2016. godine u SAD su duplirani⁴. Najveći doprinos u navedenim troškovima ima dijabetesna nefropatija (DN)⁴. Prema podacima iz Godišnjeg izveštaja o lečenju dijalizama i transplantaciji u Srbiji³ iz 2015. godine, više od polovine slučajeva terminalne bubrežne bolesti posledica su hipertenzije i dijabetesa. Dijabetesna retinopatija (DR) je najčešći pojedinačni uzrok slepila među radno sposobnim stanovništvom u Velikoj Britaniji⁵. Procenjuje se da je procenat slepih osoba usled progresivne dijabetesne retinopatije i makulopatije 3,1% u Centralnoj i 4,9% u Istočnoj Evropi⁶. Ekonomske posledice oštećenja i trajnog gubitka vida usled navedenih bolesti, odražavaju se na obolele i na članove njihovih porodica, ali i na zdravstveni sistem i društvo u celini⁶.

Razvoj dijabetesne nefropatije prolazi kroz nekoliko faza. Bolest počinje glomerularnom hiperfiltracijom, slede albuminurija i proteinurija koje dovode do pada glomerularne filtracije i progresije u hroničnu bubrežnu insuficijenciju^{3,7}. Dijabetesna retinopatija počinje gubitkom pericita i istanjeњem bazalne vaskularne membrane, mikroaneurizmama i neovaskularizacijom, koje dovode do nastanka prvo neproliferativne, a zatim proliferativne retinopatije i makularnog edema sa posledičnim oštećenjima, pa i potpunim gubitkom vida^{8,9}. Savremena istraživanja su pokazala da se u osnovi mikrovaskularnih komplikacija dijabetesa nalazi nekoliko mehanizama^{3,8,9,10}. Neki od njih su aktivacija protein kinaza C, DAG-PKC i poliolnog puta, oksidativni stres i neenzimska glikozilacija sa stvaranjem krajnjih produkata glikozilacije - AGE^{3,8,9,10}. Nastanak i progresiju mikrovaskularnih procesa na bubregu usporava renalna atrijsalna stenoza - RAS blokada, smanjivanjem kapilarnog pritiska u glomerulima^{3,10}. Takođe, RAS blokada odlaže i usporava progresiju promena na retini, i to ne samo snižavanjem krvnog pritiska^{3,8,9,10}.

Većina faktora rizika su zajednički za mikrovaskularne komplikacije dijabetesa^{3,5}. Pored genetske predispozicije, presudan faktor za razvoj dijabetesne nefropatije i retinopatije je nekontrolisana hronična hiperglikemija^{3,5,11}. Ostali faktori rizika za dijabetesnu retinopatiju su trajanje bolesti, muški

Introduction

The modern world is overwhelmed with diabetes mellitus epidemic and it's becoming a serious burden for the society as a whole.¹ Diabetes prevalence is ever increasing in all European regions.² The number of diseased increased from 8.6% in 2010 to 13.3% in 2017 in Serbia.² More than 90% of diabetic patients in Serbia suffer from type 2 diabetes mellitus.³ It is estimated that one-third of the patients already have some disease complication, at the moment of diagnosing. The majority of the death outcomes are the consequence of macrovascular complications, but microvascular complications are as important because they play a major role in disability caused by diabetes.¹

Costs of chronic kidney disease (CKD) treatment doubled in the United States from 2006-2016.⁴ The majority of the costs are due to diabetic nephropathy.⁴ According to the Annual report on dialysis treatment and transplantation in Serbia³, in 2015, more than half of the cases with terminal kidney disease were due to hypertension or diabetes. Diabetic retinopathy is the most frequent singular cause of blindness among working people in Great Britain.⁵ The estimated number of blind persons, due to diabetic retinopathy and maculopathy is 3.1% in Central and 4.9% in Eastern Europe.⁶ Economic consequences, due to vision damage or total loss caused by diabetes are affecting the diseased and their family members, as well as, health systems and society as a whole.⁶

The progression of diabetic nephropathy goes through several phases. The disease starts with glomerular hyperfiltration, followed by albuminuria and proteinuria, which lead to the fall in glomerular filtration and progression of chronic kidney failure.^{3,7} Diabetic retinopathy starts with the loss of pericytes and thinning of the basal vascular membrane, forming of microaneurysms and neovascularization. It leads to non-proliferative, at first, and then proliferative retinopathy and macular edema with consequential damages and even vision loss.^{8,9} Modern studies showed there are several mechanisms in the core of microvascular diabetic complications.^{3,8,9,10} Some of them are the activation of protein kinases C, DAG-PKC, and polyol pathway, oxidative stress and non-enzyme glucosylation with the final product - AGE^{3,8,9,10} RAS blockage slows down the appearance and progression of microvascular complications in the kidney by decreasing capillary pressure in the glomeruli.^{3,10} RAS blockage also postpones and slows down the progression of retinal damage and not only by lowering blood pressure.^{3,8,9,10}

Most risk factors for microvascular diabetic complications are common.^{3,5} Beside genetic predisposition, the key factor in the development of diabetic nephropathy and retinopathy is chronic hyperglycemia.^{3,5,11} Other risk factors for diabetic retinopathy are the duration of the disease, male gender, hypertension, smoking, and obesity.^{5,12,13} Same risk factors apply to diabetic nephropathy as well, with the addition of

pol, povišen krvni pritisak, pušenje i gojaznost^{5,12,13}. Kada je dijabetesna nefropatija u pitanju, pored navedenih faktora uticaj na razvoj i progresiju bolesti ima i hiperproteinska ishrana³. Retinopatija, sama po sebi, predstavlja nezavisan faktor rizika za ishod dijabetesne nefropatije¹⁴. Na većinu navedenih faktora mogu uticati lekari u primarnoj zdravstvenoj zaštiti^{8,15,16}. U ovom istraživanju ispitivali smo upravo mere koje su izabrani lekari preduzeli radi sprečavanja progresije dijabetesne nefropatije i retinopatije

Cilj rada

Utvrditi učestalost dijabetesne nefropatije i retinopatije i mere koje su izabrani lekari preduzeli radi sprečavanja daljeg napredovanja mikrovaskularnih komplikacija, a koje se ne odnose na glikoregulaciju.

Metod

Istraživanje je sprovedeno kao *studija preseka* u novembru 2017. godine, na uzorku od 100 pacijenata Savetovališta za dijabetes Doma zdravlja Zemun. Podaci su preuzeti iz dijabetoloških kartona stotinu pacijenata koji su došli na pregled u Savetovalište tog meseca. Uzeti su podaci iz protokola zabeleženi pri prvoj poseti, pre intervencije lekara. Podaci iz protokola dobijeni su iz razgovora sa pacijentima, fizikalnog pregleda i preuzimanjem podataka iz elektronskog kartona.

Prikupljeni su podaci koji se odnose na pol i starost ispitanika, tip dijabetesa, trajanje bolesti i prisustvo/odsustvo faktora rizika za mikrovaskularne komplikacije. Od laboratorijskih parametara, beležen je nivo kreatinina i procenjena je jačina glomerularne filtracije (JGF) na osnovu *MDRD (Modification of Diet in Renal Disease)* formule, kao i proteinurije. Prisustvo proteinurije u urinu, bez obzira na stepen bubrežne slabosti, označeno je kao dijabetesna nefropatija¹⁷. Za graničnu vrednost hronične bubrežne bolesti uzeta je jačina glomerularne filtracije od $60 \text{ ml/min/1.73m}^2$. Vrednosti niže od navedene označene su kao *hronična bubrežna insuficijencija*¹⁷. Mere za sprečavanje progresije dijabetesne nefropatije: praćeni su uključivanje inhibitora angiotenzin konvertujućeg enzima ili antagonista receptora angiotenzina (*ACEI/ARB*) u terapiju od strane izabranih lekara i upućivanje nefrologu, dok je kao mera rane detekcije i zaustavljanja napredovanja dijabetesne retinopatije posmatrano upućivanje pacijenata oftalmologu. Prisustvo/odsustvo dijabetesne retinopatije beleženo je na osnovu izveštaja oftalmologa. Podaci su obrađeni metodima deskriptivne i analitičke statistike. Povezanost sociodemografskih podataka sa mikrovaskularnim komplikacijama ispitivana je Spirmanovim testom korelacije, dok su razlike u merama koje su preduzeli izabrani lekari u grupi ispitanika sa mikrovaskularnim komplikacijama i bez njih ispitivane χ^2 -testom. Statistička značajnost definisana je na nivou verovatnoće nulte hipoteze $p \leq 0,05$.

hyper protein nutrition.³ Retinopathy, in itself, is an independent risk factor for diabetic nephropathy outcome.¹⁴ GPs may influence the majority of risk factors.^{8,15,16} This research was about the measures undertaken by the GPs, in order to prevent diabetic retinopathy and nephropathy.

Objective

Establish the incidence of diabetic nephropathy and retinopathy and review the measures GPs undertook to stop the further microvascular complications advance (but not the ones related to glucose measurement).

Method

The research was performed as a cross-sectional study in November 2017, on 100 patients in the Counseling center for diabetes, Primary Health care Center, Zemun. Data were taken from the patients' diabetic medical charts and reviewed. They were taken at the patient's first visit, before a physician's intervention. The data were acquired through a patient interview, physical examination and consulting already existing data in patient's electronic medical health records.

Data apply to age, gender, diabetes type, disease duration, and presence/absence of risk factors for microvascular complications. We took into consideration these lab results: creatinine level, glomerular filtration rate (GFR), calculated with MDRD formula, and proteinuria. Proteinuria findings, no matter what was the stage of CKD, was considered diabetic nephropathy.¹⁷ The threshold for CKD was $60 \text{ ml/min/1.73m}^2$. The values lower than this one, were considered CKD.¹⁷ Measures for preventing the progression of diabetic nephropathy, that we followed were: GPs starting ACEI/ARB therapy in these patients and nephrologist referral. As a measure of early detection and stalling diabetic retinopathy progression we followed patients' ophthalmologist referral. The presence/absence of diabetic retinopathy was confirmed after the ophthalmologist referral. The data were processed using descriptive and analytical statistics. The connection between sociodemographic data and microvascular complications was examined using the Spearman's correlation test, while the differences in the measures undertaken by GPs in the groups of the participants with and without microvascular complications were analyzed using χ^2 -test. Statistical significance was defined at the null hypothesis possibility level ($p \leq 0.05$).

Rezultati

Najveći broj ispitanika u našem uzorku bio je stariji od 65 godina (64%), a samo dva ispitanika mlađa od 35 godina. Prosečna starost ispitanika bila je 65,3 godine. Ako se posmatra tip dijabetesa, 99% ispitanika bolovalo je od dijabetesa tip 2, a samo jedan od dijabetesa tip 1. Prosečno trajanje dijabetesa iznosilo je 7,7 godina. U 71 ispitanika bolest je trajala kraće od 10 godina, u 21 ispitanika kraće od dvadeset godina, a u dva ispitanika bolest trajala 30 i više godina. Pripadnica ženskog pola bilo je 67%, a muškog pola 37%, (Tabela 1).

Table 1. Distribution of participants by gender, in relation to age and duration of diabetes

Tabela 1. Distribucija ispitanika po polu u odnosu na godine starosti i trajanje dijabetesa

Participants' age (years)	Males	Females	Total
20-35	1	1	2
35-45	1	0	1
45-55	4	5	9
55-65	10	14	24
65-75	17	33	50
>75	4	10	14
Diabetes duration (years)			
<10	29	42	71
10-20	7	14	21
20-30	1	5	6
>=30	0	2	2
Total	37	63	100

Dijabetesnu nefropatiju je imalo 15 ispitanika (15% od ukupnog broja ispitanika), od kojih je šestoro imalo i pad glomerularne filtracije ispod $60 \text{ ml/min/1,73m}^2$, tj. hroničnu bubrežnu insuficijenciju trećeg stepena. Od 100 ispitanika, 19 je imalo pad glomerularne filtracije ispod $60 \text{ ml/min/1,73m}^2$. Podatak o vrednosti kreatinina nedostaje kod jednog ispitanika. U slučaju dijabetesne retinopatije, od posmatranih 100 pacijenata pregled oftalmologa obavilo je 69, od kojih je kod 10 utvrđena dijabetesna retinopatija.

Prema starosnoj strukturi pacijenata kod kojih je utvrđeno prisustvo dijabetesne nefropatije, dva pacijenta su mlađa od 65 godina (13,3%), četvero starije od 75 (26,7%), a najveći broj pacijenata - 9 (60%) imali su između 65 i 75 godina. Kod 11 (73,3%) pacijenata sa DN bolest je trajala manje od deset godina, (Tabela 2).

Od stotinu posmatranih pacijenata, kod 69 je izvršen pregled očnog dna i utvrđena dijabetesna retinopatija kod 10, od kojih su tri pacijenta mlađa od 65 godina (30%), od

Results

The majority of the participants in our group were older than 65 (64%) and only two participants younger than 35. The average age of the participants was 65.3 years. As far as diabetes type goes, 99% were diabetes type 2 patients and only 1% type 1. The average duration of the disease was 7.7 years. In 71 participants the disease lasted less than 10 years, in 21 less than 20 years, while in two participants it lasted 30 years and longer. There were 67% of women and 37% of men, (Table 1).

Diabetic nephropathy (DN) was found in 15 participants (15%), out of whom 6 had GFR below $60 \text{ ml/min/1.73m}^2$, which translates into CKD stage 3. Out of a hundred participants, 19 had GFR less than $60 \text{ ml/min/1.73m}^2$. The datum on creatinine level is missing in one participant. As for diabetic retinopathy, out of 100 participants, 69 visited the ophthalmologist and in 10 patients retinopathy was confirmed.

In patients with diabetic nephropathy, two were younger than 65 years (13.3%), four older than 75 (26.7%), while the majority of the patients with nephropathy 9 (60%) were ages between 65 and 75. There were 6 men (40%) and 9 women (60%). In 11 patients (73.3%) with diabetic nephropathy, the disease lasted less than 10 years. (Table 2)

Fundus exam was performed in 69 patients and diabetic retinopathy (DR) was found in 10 patients. Out of the ten of them, 3 were younger than 65 (30%), 5 between ages 65 and 75 (50%), and 2 were older than 75 (20%). There were 2 men (20%) and 8 women (80%). When we compared retinopathy

65 do 75 godina - 5 (50%), starijih od 75 godina 2 (20%). Dvojica ispitanika (20%) su muškarci, a 8 (80%) žene. Prema učestalosti retinopatije u odnosu na trajanje bolesti, kod najvećeg broja pacijenata sa retinopatijom - 5 (50%) bolest je trajala između 10 i 20 godina, kod 4 (40%) kraće od 10 godina, dok je kod jednog ispitanika sa retinopatijom bolest trajala 30 i više godina, (Tabela 2).

U posmatranom uzorku, 19 pacijenata je imalo procenjeniju jačinu glomerularne filtracije manju od $60 \text{ ml/min/1.73m}^2$ (hroničnu bubrežnu insuficijenciju trećeg stepena), pri čemu niko od njih nije imao JGF manju od $30 \text{ ml/min/1.73m}^2$. Od 19 pacijenata sa smanjenom JGF, šestoro je istovremeno imalo i proteinuriju, te se oštećenje bubrežne funkcije može smatrati posledicom dijabetesne nefropatije. Svi ispitanici sa HBB stariji su od 65 godina. Od 19 ispitanika sa HBB, 13 su žene (68,4%). Takođe, kod 13 ispitanika sa HBB dijabetes traje kraće od 10 godina, (Tabela 2).

incidence and diabetes duration, we found that in the majority – 5 (50%), diabetes lasted between 10 and 20 years. In 4 patients (40%), the disease lasted less than 10 years, while in 1 participant over 30 years, (Table 2)

There were 19 patients with GFR less than $60 \text{ ml/min/1.73m}^2$ (CKD, stage 3), but none of them had GFR less than $30 \text{ ml/min/1.73m}^2$. Out of these 19 patients, 6 had proteinuria as well, so CKD was considered the consequence of diabetic nephropathy. All the participants with CKD were older than 65. Out of all CKD patients, 13 were women (68.4%). In 13 patients with CKD, diabetes lasted less than 10 years, (Table 2).

Table 2. Frequency of microvascular complications and chronic kidney disease in relation to age, gender and duration of diabetes

Tabela 2. Učestalost mikrovaskularnih komplikacija i hronične bolesti bubrega u odnosu na starost, pol i trajanje dijabetesa

Age (years)	DN	%*	Without DN	%*	DR	%*	Without DR	%*	CKD	%*	Without CKD	%*
<65	2	13.3	34	40.5	3	30.0	20	33.9	0	0	36	45
65-75	9	60	43	51.2	5	50.0	30	50.8	13	68.4	37	46.2
>75	4	26.7	7	8.3	2	20.0	9	15.2	6	31.6	7	8.8
Gender												
Male	6	40	30	35.7	2	20.0	22	37.9	6	31.6	31	38.8
Female	9	60	54	64.3	8	80.0	37	62.1	13	68.4	49	61.2
Diabetes duration												
<10	11	73.3	60	71.4	4	40.0	43	72.9	13	68.4	58	72.5
10-20	2	13.3	19	22.6	5	50.0	11	18.6	4	21	17	21.2
20-30	1	6.7	4	4.8	0	0	4	6.8	1	5.3	4	5
30-40	1	6.7	1	1.2	1	10.0	1	1.7	1	5.3	1	1.3
Total	15	100	84	100	10	100	59	100	19	100	80	100

* % percentage of participants compared to the total number of the participants, with or without the marked characteristic
DN – diabetic nephropathy; DR – diabetic retinopathy; CKD – chronic kidney disease

Analizom međusobnog odnosa između starosti i pola ispitanika, kao i dužine trajanja dijabetesa, utvrđena je slaba pozitivna korelacija između trajanja dijabetesa i retinopatije ($p<0,05$) i umerena pozitivna korelacija između starosti ispitanika i hronične bubrežne bolesti ($p<0,01$). Vrednosti koeficijenata Spirmanove korelacije za posmatrana obeležja, prikazane su u Tabeli 3.

Analyzing the relation between age and gender, as well as disease duration, we found a weak positive correlation between diabetes duration and diabetic retinopathy ($p<0.05$) and moderate positive correlation between participants' age and CKD ($p<0.01$). Coefficients for Spearman's correlation, for the marked characteristics, are shown in Table 3.

Table 3. Coefficients of the Spearman's correlation between the socio-demographic data of the participants and the appearance of microvascular complications in diabetes

Tabela 3. Koeficijenti Spirmanove korelacije između sociodemografskih podataka ispitanika i pojave mikrovaskularnih komplikacija dijabetesa

	DN	DR	CKD
Age	0.164	0.083	0.581**
Gender	0.032	-0.146	-0.035
Diabetes duration	0.069	0.303*	0.119

*p<0.05, **p<0.01

DN – diabetic nephropathy; DR – diabetic retinopathy; CKD – chronic kidney disease

Kao mere koje su izabrani lekari preduzeli radi ranog otkrivanja i sprečavanja progresije mikrovaskularnih komplikacija, posmatrani su uključivanje ACEI/ARB u terapiju, upućivanje pacijenata na oftalmološki i nefrološki pregled. Odnos upućivanja nefrologu i oftalmologu je daleko pomećen u korist oftalmoloških konsultacija. Ukupan broj upućenih nefrologu je troje (3%), a oftalmologu 69 (69%) ispitanika.

Od 15 ispitanika sa dijabetesnom nefropatijom (Tabela 4), nefrologu je upućeno dvoje (13,3%), dok je od ispitanika iz grupe bez nefropatije nefrologu upućen jedan ispitanik (1,2%).

Od svih pacijenata sa dijabetesnom nefropatijom, 10 (66,7%) je upućeno na oftalmološki pregled. Iz grupe ispitanika koji nemaju nefropatiju, na oftalmološki pregled upućeno je 59 (69,4%). U odnosu na broj ispitanika upućenih iz grupe bez DN, postoji statistički značajna razlika ($p<0,001$) kada su u pitanju i upućivanje oftalmologu i nefrologu. Kada se analizira mera preveniranja progresije bubrežne bolesti, u smislu dodavanja lekova iz grupe ACEI ili ARB, u našem uzorku ACEI/ARB dobilo je 11 pacijenata sa DN (73,3%), što je veći procenat od zastupljenosti ACEI/ARB u grupi bez dijabetesne nefropatije - u ovoj grupi pomenute lekove koristi 55 (64,7%) ispitanika. Postoji statistički značajna razlika u broju ispitanika koji koriste ACEI/ARB u grupi ispitanika sa dijabetesnom nefropatijom, u odnosu na grupu bez nefropatije ($p<0,001$), Tabela 4.

We looked at starting ACEI/ARB therapy, referral to an ophthalmologist or nephrologist, as the measures undertaken by GPs to detect and prevent progression of microvascular complications. The relation between ophthalmologist and nephrologist referral is in favor of the ophthalmologists. The total number of the participants referred to a nephrologist was 3 (3%) and 69 patients (69%) were referred to an ophthalmologist.

Out of 15 patients with diabetic nephropathy (Table 4), 2 were referred to a nephrologist (13.3%). Out of the group without nephropathy, only one patient was referred to a nephrologist (1.2%). Among the patients with diabetic nephropathy, 10 were referred to an ophthalmologist (66.7%). Out of the group without nephropathy, 59 were referred to an ophthalmologist (69.4%). We found a statistically significant difference ($p<0.001$) in the group without DN, in relation to ophthalmologist or nephrologist referral. Analyzing preventive measures to stop CKD, we found that 11 patients with DN (73.3%) received ACEI/ARB medication, which is higher than in the group without DN, 55 patients (64.7%). There is a statistically significant difference ($p<0.001$) in the number of patients using ACEI/ARB between the groups with or without DN, Table 4.

Table 4. Measures undertaken by GPs to prevent the progression of microvascular complications of diabetes, in participants with and without diabetic nephropathy

Tabela 4. Mere sprovedene od strane izabranih lekara radi sprečavanja progresije mikrovaskularnih komplikacija kod ispitanika sa/bez dijabetesne nefropatije

	With DN	%**	Without DN	%**	χ^2
ACEI/ARB ⁺	11	73.3	55	64.7	10.240*
ACEI/ARB ⁻	4	26.7	30	35.3	
Referred to an ophthalmologist	10	66.7	59	69.4	32.914*
Not referred to an ophthalmologist	5	33.3	26	30.6	
Referred to a nephrologist	2	13.3	1	1.2	87.364*
Not referred to a nephrologist	13	86.7	83	97.6	

*p < 0.001

** % of the participants in relation to the total number of the participants, with or without the marked characteristic

DN – diabetic nephropathy; DR – diabetic retinopathy; ACEI/ARB – angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Dva ispitanika upućena nefrologu imala su JGF < 45 ml/min/1.73m², dok je jedan imao JGF = 50 ml/min/1.73m².

Procenat pacijenata koji imaju retinopatiju značajno je veći u grupi obolelih od dijabetesne nefropatije (26,7%), u odnosu na grupu bez nefropatije (7,1%). Ukupna učestalost retinopatije u našem uzorku iznosi 14,5% od broja pacijenata (69%) koji su podvrgnuti oftalmološkom pregledu.

Diskusija

U našem istraživanju mikrovaskularnu komplikaciju u vidu dijabetesne nefropatije imalo je 15% od ukupnog broja ispitivanih dijabetičara. Dijagnoza DN postavljena je na osnovu nalaza proteinurije u urinu. Od ukupnog broja pacijenata sa proteinurijom, šestoro je imalo i pad JGF ispod 60 ml/min/1.73m². U studiji rađenoj u Francuskoj¹⁸, oštećenje bubrega imalo je 57% a manifestnu proteinuriju 16%; HBB je imalo 29% ispitanika¹⁸. U UKPDS (*United Kingdom Prospective Study of Diabetes*) studiji¹⁹ albuminurija je otkrivena kod 38% ispitanika, a smanjenje JGF ispod 60 ml/min/1.73m² kod 29% ispitanika. U studiji iz Finske²⁰ procenat dijabetesne nefropatije, sa ili bez oštećenja JGF, iznosi visokih 68,6%, ali je zastupljenost proteinurije tek 7,2%, a procenat smanjenja JGF je 16,2%. U našoj studiji, prisustvo DN je manje nego u Francuskoj i Finskoj studiji, sa napomenom da je u obe studije rađeno utvrđivanje albuminurije u uzorku urina, dok je procenat pacijenata sa proteinurijom sličan onom u Francuskoj, a upola manji od procenta pacijenata sa proteinurijom u Finskoj^{18,20}. Relativno niska zastupljenost DN u našem uzorku može se objasniti upravo nemogućnošću određivanja albuminurije kao ranog markera oštećenja bubrega u dijabetesu^{3,21,22}. Značaj određivanja albuminurije još je veći kada se zna da je ona marker ne samo bubrežnog oštećenja, već i ukupnog kardiovaskularnog rizika^{3,21}. Mogućnost otkrića albuminurije kao ranog markera oštećenja bubrega, može biti razlog za manju učestalost HBB, tj. pada JGF u zemljama u kojima je određivanje albuminurije moguće na primarnom nivou zdravstvene zaštite^{18,20}. Otkriće strukturnog oštećenja bubrega u početnoj fazi, omogućava blagovremenu preventivnu reakciju u smislu korekcije promenljivih faktora rizika za dijabetesom uzrokovanu hroničnu bubrežnu bolest^{3,15,19,21}. Od pacijenata kod kojih je utvrđena hronična bubrežna bolest nefrologu je upućeno troje, od toga dvoje sa proteinurijom. Svi su bili u trećem stadijumu HBB, dvoje sa JGF < 45 ml/min/1.73m². U studiji iz 2015. godine sprovedenoj u SAD²³, procenat upućenih nefrologu iznosio je 11% i blizak je vrednosti dobijenoj u našem istraživanju. Pacijenti iz ove studije upućivani su nefrologu na JGF oko 46 ml/min/1.73m², što je u saglasnosti sa našim rezultatima²³.

Manji broj upućenih na konsultaciju nefrologu u našoj studiji nije u suprotnosti sa preporukama Američke dijabetološke asocijacije²² i onih iz Nacionalnog vodiča za prevenciju, dijagnostikovanje i praćenje hronične bubrežne

Two participants who were referred to a nephrologist had GFR < 45 ml/min/1.73m², while one had GFR of 50 ml/min/1.73m².

The percentage of patients with retinopathy was much higher in the group with nephropathy (26.7%) than in the group without nephropathy (7.1%). The total incidence of diabetic retinopathy was 14.5%, out of the total number of patients referred to an ophthalmologist (69%).

Discussion

Diabetic nephropathy, as a microvascular complication was found in 15% of our participants. DN was diagnosed based on proteinuria findings. Out of the total number of patients with proteinuria, 6 had GFR < 60ml/min/1.73m². In a French study¹⁸, 57% of the participants had kidney damage, while manifest proteinuria was found in 16% of patients. CKD was found in 29% of the participants¹⁸. In UKPDS study, albuminuria was detected in 38% of the participants, while GFR < 60ml/min/1.73m² in 29%. In Finish study²⁰, percentage of DN with or without GFR changes was 68.6%, but proteinuria was found only in 7.2% of the participants and GFR decline in 16.2%. The percentage of DN in our study is lesser than in French and Finish study. In both studies, proteinuria detection was performed, and while the percentage of proteinuria was similar to the one in French study findings, it was twice as smaller than in the Finish study.^{18,20} Relatively low incidence of DN in our study may be due to our lack of resources to perform albuminuria lab analysis since albuminuria is an early marker of kidney damage in diabetes.^{3,21,22} The importance of albuminuria detection is even higher considering that it's not only the marker of kidney damage, but also of the total cardiovascular risk.^{3,21} Being able to perform albuminuria detection, at primary health care level, may be the reason why in our study CKD incidence and GFR decline were lower.^{18,20} Detection of kidney damage in the early stages allows a timely reaction to correct modifiable risk factors for diabetes caused CKD.^{3,15,19,21} Out of all patients with diagnosed CKD, 3 were referred to a nephrologist and out of them, 2 had proteinuria. All of them had stage 3 CKD, 2 with GFR < 45 ml/min/1.73m². In USA study²³, from 2015, the percentage of the patients referred to a nephrologist was 11% and it was close to our findings. Patients from their study were referred when GFR was lower than 46 ml/min/1.73m², and it correlates to our results.²³

The smaller number of the nephrologist referred patients in our study correlates with ADA (American Diabetes Association)²² guidelines as well as our National guidelines for prevention, diagnosing and follow up of CKD.¹⁷ The aforementioned guidelines^{17,21} stress that the nephrologist exam is necessary when GFR ≤ 30 ml/min/1.73m², but there were no such patients in our study. One other possible reason for the small number of nephrologist referred patients was that at the

bolesti¹⁷. U navedenim preporukama^{17,22} pregled nefrologa je obavezan kod JGF $\leq 30 \text{ ml/min/1.73m}^2$, a takvih pacijenata nije bilo u našem uzorku. Još jedan mogući razlog manjeg broja ispitanika upućenih nefrologu može biti i to što je istraživanje rađeno u vreme implementacije integrisanog informacionog sistema (IZIS) u zdravstveni sistem (www.mojdoktor.gov.rs), te u posmatranom periodu dostupnost specijalističkih službi na višim nivoima zdravstvene zaštite nije bila na zadovoljavajućem nivou.

Bez obzira da li su pacijenta upućivali nefrologu ili ne, izabrani lekari, prema našim rezultatima, učinili su napor da preveniraju^{3,10,24,25} progresiju bubrežne bolesti kod pacijenata sa dijabetesom. Preko polovine pacijenata sa dijabetesom i hipertenzijom dobilo je u terapiji ACEI/ARB. U grupi pacijenata sa dijabetesnom nefropatijom procenat pacijenata sa ACEI/ARB u terapiji je veći nego u grupi bez nje. U studiji rađenoj u Bostonu, upotreba ACEI/ARB radi zaustavljanja progresije HBB od strane izabranih lekara iznosila je 65%, dok je pod nadzorom nefrologa ovaj procenat povećan na 85%²³. U studiji rađenoj na nacionalnom uzorku u SAD²⁶, upotreba ACEI/ARB kod dijabetičara sa hipertenzijom iznosila je niskih 40,7%. U studiji rađenoj u Kini²⁷ 2015. godine, procenat pacijenata na terapiji ACEI/ARB takođe je manji od polovine ispitivanih i iznosi 48,3%. Ovi procenti su znatno niži od zastupljenosti ACEI/ARB u dijabetičara iz našeg uzorka, bez obzira da li su imali proteinuriju ili ne.

Dijabetesnu retinopatiju u našem uzorku imalo je 10 pacijenata. Učestalost retinopatije značajno je veća u grupi ispitanika sa dijabetesnom nefropatijom, što je i očekivano budući da su veoma često ove komplikacije udružene²⁸. U istraživanjima koja su se bavila testiranjem na dijabetesnu retinopatiju, učestalost ove komplikacije iznosila je 20,3% u Severnoj Karolini²⁸, 24,6% u Libanu²⁹ i 26% u Irskoj³⁰. Relativno mala učestalost retinopatije u našem uzorku može se objasniti kraćim trajanjem dijabetesa kod najvećeg broja ispitanika^{28,29}. Daleko veći broj ispitanika je upućen oftalmologu nego nefrologu, delimično zato što je konsultacija oftalmologa dostupna na primarnom nivou zdravstvene zaštite. Procenat ispitivanih značajno je veći od procenta obuhvaćenih skriningom u studijama širom sveta. Tako je procenat u Australiji³¹ 22%-53%, u već pomenutoj Severnoj Karolini²⁸ 26,5% pre i 40,4% posle organizovanog skrininga, dok je u studiji u Irskoj³⁰ 49% osoba obuhvaćeno skriningom.

Postoje i istraživanja u kojima je procenat ispitivanih veći od procenta u našoj studiji - u holandskoj studiji iz 2012. godine³² obuhvat pacijenata skriningom na DR iznosi impresivnih 81%. Više od trećine ispitanika iz obe grupe (sa i bez DN) u našem istraživanju nije pregledano od strane oftalmologa, što je nezadovoljavajući podatak. Delimično je to moguće objasniti nedostatkom termina za pregled kod oftalmologa usled implementacije IZIS-a (www.mojdoktor.gov.rs). Međutim, podaci iz literature govore da je problem upućivanja na oftalmološki pregled prisutan i u drugim zdravstvenim

time of our study the nephrologists were quite unavailable due to the implementation of the Integrated information system in our health care system (www.mojdoktor.gov.rs). The available appointments were scarce for other specialties as well.

Whether a patient was referred to a nephrologist or not, GPs made an effort to prevent the progression of CKD in diabetic patients, according to our study findings.^{3,10,24,25} Over half of the patients with diabetes and hypertension were started on ACEI/ARB medications. In the group with diabetic nephropathy, the percentage of patients taking ACEI/ARB was higher than in the group without nephropathy. In the Boston study, the GPs percentage starting ACEI/ARB therapy in order to stop the progression of CKD was 65% and with the nephrologist consultation, this number rose to 85%.²³ The USA study, performed on the national level²⁶ found that the use of ACEI/ARB in hypertensive diabetic patients was rather low at 40.7%. In a Chinese study,²⁷ from 2015 the number of diabetic patients using ACEI/ARB was 48.3%, which is low as well. These percentages were lower than in our study, whether the patients had proteinuria or not.

There were 10 patients with diabetic retinopathy in our study. The incidence of retinopathy was significantly higher in the group with diabetic nephropathy, which was expected considering these two complications often go hand in hand.²⁸ The studies focusing on diabetic retinopathy screening found that the incidence of this complication was 20.3% in North Caroline²⁸, 24.6% in Lebanon²⁹, and 26% in Ireland³⁰. Relatively small incidence of retinopathy in our sample may be due to shorter diabetes duration in our participants.^{28,29} Significantly higher number of the participants was referred to an ophthalmologist than a nephrologist, partially because the ophthalmologist consultation is often available at the primary health care level, in our country. The percentage of the patients screened for diabetic retinopathy was significantly higher than in any other study in the world. The percentage of patients screened for retinopathy in Australia³¹ was 22-53%, in North Caroline²⁸ 26.5% before the organized screening and 40.4% after, while in Ireland³⁰ this number was 49%. There are studies with a much higher number of screened patients than in ours, such as the Dutch study from 2012 when 81% of the participants were screened for diabetic retinopathy.³² More than the third of our participants (with or without DR) were not examined by an ophthalmologist, which is unsatisfactory. One of the possible explanations is the insufficient number of the available ophthalmologist's appointments in our Integrated information system (www.mojdoktor.gov.rs). But literature data show that ophthalmologist referral is a problem in other parts of the world as well.^{33,34} In the study which researched barriers for retinopathy screening, physicians from 41 countries were included.³³ Beside patients related factors, such as low awareness of the importance of this sort of examination and low level of health literacy, the physicians em-

sistemima^{33,34}. U studiji u kojoj su ispitivani stavovi u vezi sa preprekama za obavljanje skrining pregleda na retinopatiju kod lekara iz 41 države u svetu³³, pored faktora u vezi sa pacijentima, a koji se, uglavnom, odnose na nedovoljnu svest o značaju ovog pregleda i nizak nivo zdravstvene pismenosti, kao vodeće prepreke u samim zdravstvenim sistemima lekari su naveli probleme prilikom upućivanja na specijalistički pregled i dugo vreme čekanja na te preglede. Analizom 77 studija koje su se bavile barijerama i faktorima koji bi pospešili odziv na skrining za dijabetesnu retinopatiju u primarnoj zdravstvenoj zaštiti, kao vodeće prepreke navedene su iste stavke³⁴.

U našoj studiji postoji nekoliko ograničenja. Rađena je kao studija preseka, na relativno malom uzorku, tako da postoje ograničenja u smislu njene reprezentativnosti. Pouzdanost statističke analize ograničena je malim brojem posmatranih ispitanika. Buduća studija na većem uzorku će omogućiti pouzdaniju analizu povezanosti faktora rizika sa mikrovaskularnim komplikacijama dijabetesa. Takođe, u ovom radu nije procenjivan uticaj glikoregulacije u zaustavljanju progresije mikrovaskularnih komplikacija, što otvara mogućnost da se u budućem istraživanju ispita glikoregulacija kao ključni faktor rizika za razvoj dijabetesne nefropatije i retinopatije. Učestalost dijabetesne nefropatije bila bi veća da je postojala mogućnost određivanja albuminurije ili odnosa albumin/kreatinin kod ispitivanih pacijenata sa dijabetesom. Takođe, nije moguće pratiti efikasnost primenjenih mera koje su predmet posmatranja.

Uprkos navedenim ograničenjima, značaj ove studije ogleda se u tome što posmatra mikrovaskularne komplikacije dijabetesa iz ugla izabranog lekara na nivou primarne zdravstvene zaštite, i sagledava mogućnosti i ograničenja sa kojima se oni susreću u svakodnevnom radu sa pacijentima obolelim od dijabetesa. Takođe, skreće pažnju na značaj preventivnih mera u sprečavanju nastanka i progresije hroničnih komplikacija dijabetesa, i potrebu da se određene dijagnostičke procedure obavljaju na primarnom nivou zdravstvene zaštite. Podrazumeva neophodnost posmatranja pacijenata obolelih od dijabetesa sveobuhvatno, pristupajući im dovoljno agresivno u smislu smanjivanja faktora rizika, od kojih su mnogi povezani sa životnim stilom i gotovo isključivo u nadležnosti izabranih lekara.

Zaključak

Učestalost dijabetesne nefropatije u uzorku od 100 pacijenata pregledanih u Savetovalištu za dijabetes Doma zdravlja Zemun iznosi 15%, a učestalost dijabetesne retinopatije 14,5%. U cilju ranog otkrivanja dijabetesne retinopatije, izabrani lekari su uputili na testiranje 69% ispitanika iz uzorka, i uveli ACEI/ARB u terapiju kod 73,3% ispitanika kojima je dijagnostikovana dijabetesna nefropatija, kako bi spečili progresiju dijabetesne bolesti bubrega. Iako je

phasized referral problems and long waiting time. Analyzing 77 studies focused on the barriers and factors which would improve patients' better responding to retinopathy screening in primary health care, we found that the major obstacles were the same everywhere.³⁴

There are several limitations to our study. It was done as a cross-sectional study, on a relatively small sample, so there are limitations in its representativity. The reliability of the statistical analysis is also limited by the small number of participants. Some future study, on a larger number of the participants, may produce a more reliable analysis of the relation between risk factors and diabetic microvascular complications. Also, our study didn't take into consideration the influence of glucose levels, as an important risk factor for the progression of microvascular complications. This creates a possibility for a future study which would consider glucose levels as a key risk factor for diabetic nephropathy and retinopathy. The incidence of diabetic nephropathy would have been higher had there been a possibility to perform albuminuria test and albumin/creatinine ratio in our labs. Also, it wasn't possible to follow the efficacy of the undertaken measures, which were the subject of our research.

In spite of all the aforementioned limitations, the importance of this study lays in the fact that it considers diabetic microvascular complications from the GP's point of view. It also views the possibilities and limitations, GPs are met with, in their everyday practice, working with diabetic patients. It draws attention to the preventive measures which would stop and prevent chronic diabetic complications. There is also the need for some diagnostic procedures to be performed at the primary health level. Our study implies diabetic patient should be considered as a whole, should be approached aggressively enough to reduce risk factors. Many of these factors are a part of the patient's lifestyle and they are in the competence of GP.

Conclusions

The incidence of diabetic nephropathy in our sample of a hundred patients, examined in the Counseling center for diabetes, Primary Health care Center was 15% and diabetic retinopathy 14.5%. GPs referred 69% of the participants to an ophthalmologist, for the sake of retinopathy screening. They also started ACEI/ARB in 73.3% of the patients with diabetic nephropathy to prevent the progression of CKD. Although the number of nephrologist referrals was lower than ophthal-

evidentirano slabije upućivanje na nefrološke konsultacije u odnosu na oftalmološke, izabrani lekari su postupali u skladu sa preporukama Nacionalnog vodiča dobre kliničke prakse za prevenciju, dijagnostikovanje i lečenje hronične bolesti bubrega i Američke dijabetološke asocijacije. Potrebna su dalja istraživanja kojima bi se utvrdile postojeće barijere i mogućnosti za efikasniju prevenciju progresije mikrovaskularnih komplikacija dijabetesa na nivou primarne zdravstvene zaštite.

mologist, GPs made right decisions and in accordance with ADA (American Diabetes Association) guidelines as well as our National guidelines for prevention, diagnosing and follow up of CKD. Further research is needed in order to define existing barriers and find out possibilities for the more effective prevention of the progression of diabetic microvascular complications at the primary health care level.

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