Diabetic nephropathy: clinical presentation, course, and novel treatment possibilities

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Abstract

Diabetic kidney disease (DBD) is one of the major complications of diabetes (DM) and the leading cause of chronic kidney disease (CKD) worldwide. About 10% of patients with DBD progress to terminal HBB, and the rest die mostly due to cardiovascular disorders and infection even before they need treatment for kidney replacement. The main strategies to prevent the development and alleviate the progression of DBB in recent decades have been intensive glycemic control and blockade of the renin-angiotensin-aldosterone system. However, this approach did not achieve optimal results. Taking into account the increase in patients with DBB, high spending from the health care budget and the development of new therapeutic possibilities with significant kidney protection, the International Society of Nephrology issued in 2020. (Kidney Disease: Improving Global Outcomes (KDIGO) Guideline) is the first guide to treating patients with DBB. This review paper aims to point out phenotypic variability and present recent advances in the treatment of DBB.

Key words: diabetic kidney disease, phenotypic variations, treatment
### Introduction

Recently, three important nephrology societies *International Society of Nephrology – ISN, American Society of Nephrology – ASN, and European Renal Association – ERA - EDTA* published the statement that kidney diseases are a „hidden or silent epidemic“ with a global prevalence of 9.1% of CKD of all stages, which makes 697.5 million cases in the world. The majority of kidney diseases are asymptomatic and undiscovered until the late stages of the disease and CKD. At the same time, CKD has got a progressive course to the terminal phase (which requires kidney function replacement therapy), followed by significant comorbidities and shorter life expectancy. Progressive CKD, leading to grave uremic complications, is a „systemic“ disease influencing almost all organ systems.4-4

Besides hypertension, one of the leading causes of CKD in many countries is diabetes mellitus - DM. According to the World Health Organization data, there is a global pandemic of DM. The prediction is that by 2040 the prevalence of DM patients will be 642 million. Simultaneously, there’s an increase in the number of DM patients with kidney disease. Considering the increase of DM patients with CKD, high health budget costs, and the development of novel therapeutic possibilities with significant kidney protection, the International Society of nephrology published (*Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines*) the first guidelines for the treatment of patients with DM and CKD in 2020. This review paper aims to point out the phenotype variability and present recent advances in the treatment of DKD.

The kidney disease developing as a part of DM was called diabetic nephropathy (DN), until recently. This microvascular complication appears in 30% of patients with type 1 diabetes (DM1) and 40% of patients with type 2 diabetes (DM2), mostly 10–20 years from DM diagnosis. When it develops it’s an important death predictor in DM patients. In some smaller studies, the prevalence of DN goes up to 80% in patients with DM. But only 10% of these patients progress to terminal kidney disease - stage 5 CKD and the majority die even before they need kidney function replacement therapy, most often due to cardiovascular diseases and infections. Although a great improvement has been made in decreasing mortality and slowing down DN, the percentage of patients with DN progressing into the terminal phase of chronic kidney disease hasn’t significantly decreased.
Klinički tok bolesti bubrega tokom dijabetesa

Klasično, DN se definise kao klinički sindrom koji odlikuje perzistentna albuminurija (>300 mg/dan ili 300 mg/g kreatinina ili 30 mg/mmol kreatinina), progresivno smanjenje jačine glomerulske filtracije (JGF), prisustvo dijabetesne retinopatije i hipertenzije, a bez laboratorijskih i kliničkih znakova drugih bolesti bubrega ili mokraćnih puteva. Istorijski gledano, verovalo se da bolesnici počinju sa normalnom ili povišenom JGF za 20% označeno kao hiperfiltracija, pri čemu je ova faza očiglednija kod DM1 zbog hiperglikemije, a da je u merenom povećana albuminurija bila najraniji klinički detektovan biomarker. Međutim, pokazalo se da se klinička slika i tok DN razlikuju kod bolesnika sa DM1 i DM2, a da odsustvo retinopatije kod bolesnika sa DM2 ne isključuje postojanje DN. Nadalje, ispitivanja poslednjih decenija pokazala su da pored klasične kliničke slike DN, postoje bolesnici sa neklasičnom kliničkom slikom DN (Shema 1). U Shemi 1 navedene su četiri fenotske varijacije DN: 1. klasični fenotip DBB koji karakteriše uporna i visoka albuminurija i naknadno progresivno smanjenje JGF do stadiuma 5 HBB (linija 1 na Shemi 1), koji se uglavnom primećuje kod osoba sa lošom kontrolom glikemije; 2. regresija albuminurije kod bolesnika sa dijabetesnom bolest bubrega (linija 2 na Shemi 1), za koje još uvek ostaje nepoznato da li će se JGF smanjivati s vremenom; 3. bolesnici sa brzim smanjenjem - padom JGF (više od 5 ml/min/1,73m² godišnje) (putanja 3 na Shemi 1), najčešće veoma brzo razvijaju terminalnu insuficijenciju bubrega; 4. bolesnici sa sniženom JGF bez albuminurije ili proteinurije (putanja 4 na Shemi 1) koji nisu reaktivni akutnim sudarima sa onima sa proteinurijom ili albuminurijom. Ove fenotske varijacije imaju i različite histološke odlike. Pretpostavka je da su varijacija u kliničkom toku DN posledica promene u prevalenciji komorbiditeta, kao što su povećanje učestalosti hipertenzije i starosti u populaciji, smanjenje prevalencije pušenja, poboljšanje kontrole glikemije, krvnog pritiska i lipida, i upotreba antihipertenzivnih lekova koji deluju kao inhibitori renin-angiotenzin-aldosteron sistema (RAAS) i antihiperglikemika: inhibitori kotransportera natrijum-glukoze 2 (SGLT2) koji imaju renoprotektivno dejstvo i istovremeno smanjuju rizik od kardiovaskularne smrti. Ova saznanja su dovela da se sve više koristi naziv „dijabetesna bolest bubrega” ili „dijabetesna hronična bolest bubrega”, ili „bolesti bubrega tokom dijabetesa”. U skladu s tim, Američko društvo za dijabetes (American Diabetes Association - ADA) definisalo dijabetesnu bolest bubrega (DBB) prisustvom albuminurije i/ili smanjenje JGF, a u odsustvu znaka ili simptoma drugih primarnih uzroka bolesti bubrega.

The clinical course of the kidney disease in diabetes

Classically, DN is defined as a clinical syndrome characterized by persistent albuminuria (>300 mg/day or 300 mg/g of creatinine or 30 mg/mmol of creatinine), progressive decrease in glomerular filtration rate (GFR), presence of diabetic retinopathy, and hypertension, but without lab and clinical signs of other kidney diseases or urinary tract infections. Historically, it was believed the patients start with normal or 20% increased GFR, called hyperfiltration, this phase being more obvious in DM1, due to hyperglycemia, and moderately increased albuminuria was the earliest detected clinical biomarker. However, it turned out that the clinical presentation and course of DN differ between patients with DM1 and DM2, and the absence of retinopathy in patients with DM2 doesn’t exclude the presence of DN. Furthermore, the research done in the last decades showed that besides classical clinical presentation of DN, there are patients with non-classical clinical presentation of DN (Scheme 1). In Scheme 1 there are four phenotype variations of DN: 1. classical phenotype of DKD, characterized by persistent and high albuminuria, and subsequent progressive decrease in GFR, until the stage 5 of CKD (line 1 in the Scheme 1), mostly present in persons with poor glycomic control; 2. The albuminuria regression in patients with diabetes (line 2 in Scheme 1), and for those is still unknown whether GFR will decrease in time; 3. The patients with a fast decrease – drop of GFR (more than 5 ml/min/1,73m² a year) (pathway 3 in Scheme 1), and most often, very promptly, develop terminal kidney disease; and 4. The patients with decreased GFR, without albuminuria or proteinuria (pathway 4 in Scheme 1) who have got slower loss of GFR when compared to those with proteinuria or albuminuria. These phenotype variations have also got different histologic features. It is assumed that the variations in the clinical course of DN are the consequence of the change in the prevalence of comorbidities, such as an increase in the hypertension prevalence and the population age, a decrease in smoking prevalence, improvement in glyemic control, blood pressure, and lipids, and use of antihypertensive drugs which act as renin-angiotensin-aldosterone system inhibitors (RAAS), and antihyperglycemic drugs: sodium-glucose cotransporter-2 (SGLT2) inhibitors have got renoprotective properties and reduce the risk of cardiovascular death, at the same time. These findings led to more often use of the terms „diabetic kidney disease” or „chronic diabetic kidney disease”, or „kidney disease in diabetes”. In accordance, American Diabetes Association - ADA defines diabetic kidney disease (DBD) as albuminuria and/or reduced GFR, but in the absence of signs and symptoms of other primary causes of kidney disease.
1. bolesnici sa klasičnom slikom DBB, 2. bolesnici sa DBB i povlačenjem – regresijom albuminurije do normalnih vrednosti, 3. bolesnici sa sniženom JGF bez albuminurije ili proteinurije.

G1-G5 stadijumi HBB prema jačini glomerulske filtracije; JGF = jačina glomerulske filtracije.

Rizik od progresije HBB prikazan je u KDIGO vodiču iz 2012. godine (bela polja – najmanji rizik, markeri oštećenja bubrega nisu prisutni, zelena polja – najveći rizik): što je viši stadijum HBB (G1 -> G5) i veća količina albumina u mokraći (30 -> 300 mg/g kreatinina) stepen oštećenja bubrega je veći15.

**Faktori rizika za nastanak bolesti bubrega tokom dijabetesa**

Faktori rizika za nastanak DBB klasiﬁkuju se kao faktori osjetljivosti za početak (inicijaciju) i progresiju bolesti (Tabela 1)20. Neki od navedenih faktora su nepromenljivi. Od promenljivih, dva faktora su najznačajnija - hiperglikemija i hipertenzija koji pojedinačno, ali i udruženo oštećuju parenchim i funkciju bubrega. Hiperglikemija izaziva metaboličke procese i hemodinamske promene u bubregu koji dovode do disfunkcije endotelnih ćelija, glomerulske hiperfiltracije i infekcije u ranom dijabetesu. Prisustvo sistemske hipertenzije dodatno izaziva intraglomerulsku hipertenziju. Sve ovo dovodi do oštećenja glomerula, posebno u podocitima i tubulo-intersticiji, povećanja propustljivosti glomerula za albumine, fibroze, a potom i smanjenja JGF.

Primarni cilj lečenja DBB je da se spreči: porast mikroalbuminurije u makroalbuminuriju (iznad 300 mg/g ili 30 ml/min/1,73m² godišnje) (iznad 300 mg/g ili 30 ml/min/1,73m² godišnje).
of: the increase of microalbuminuria into macroalbuminuria (above 300 mg/g or 30 mg/mmol of creatinine), reduction of kidney function, and accompanying cardiovascular diseases. Accordingly, intensive glycemic control, antihypertensive treatment by blocking the RAAS system, and statin therapy which modifies lipids are a cornerstone of DBD treatment in the last quarter of the century.

Arterial hypertension is the main risk factor in the development and progression of DKD, and a permanent decrease in blood pressure is probably the most effective singular intervention for slowing down DBD progression in type 1 and 2. Hypertension is 1.5−2.0 times more common in diabetics than in non-diabetics. In patients with DM1, blood pressure values are usually normal on diagnosis, and therefore hypertension onset is intimately linked to DKD occurrence. In persons with DM2, approximately one third has high blood pressure when diabetes is first diagnosed. The prevalence of hypertension is almost 100% when DKD is manifested.

### Table 1. Risk factors for diabetic kidney disease

| Faktori/ Factors | Osetljivost/ Sensitivity | Inicijacija/ Initiation | Progresija/ Progression |
|------------------|-------------------------|------------------------|-------------------------|
| **Demografski**/ **Demographic** |                       |                        |                         |
| Starije godine/ **Older age** | +                       |                         |                         |
| Muški pol/ **Male gender** | +                       |                         |                         |
| Rasa/ **Race** | +                       |                         |                         |
| **Nasledje/ **Heritage** |                       |                        |                         |
| DBB u porodici/ **DKD in the family** | +                       | +                      |                         |
| Genetske bolesti bubrega/ **Genetic kidney diseases** | +                       | +                      |                         |
| **Sistemsni poremećaji/ **Sistemic disorders** |                       |                        |                         |
| Hiperglikemija/ **Hyperglycemia** | +                       | +                      | +                       |
| Hipertenzija/ **Hypertension** | +                       | +                      | +                       |
| Gojaznost/ **Obesity** | +                       | +                      | +                       |
| **Bubrežni poremećaji/ **Kidney disorders** |                       |                        |                         |
| Ponavljano AOB/ **Repeate AKD** | +                       | +                      | +                       |
| Toksi/ **Toxins** | +                       | +                      | +                       |
| Pušenje/ **Smoking** | +                       | +                      | +                       |
| **Dijeta/ **Diet** |                       |                        |                         |
| Veći unos belančevina/ **Higher protein intake** | +                       | +                      | +                       |

DBB = dijabetesna bolest bubrega, AOB = akutno oštećenje bubrega, DKD = diabetic kidney disease, AKD = acute kidney damage
Brojna ispitivanja su pokazala da istovremeno prisustvo hipertenzije i DDB sa albuminurijom značajno povećava rizik od dijabetičkih mikrovaskularnih komplikacija i razvoja DDB25,26. Čak i kod normotenzivnih bolesnika sa DM2 i albuminurijom, primena blokatora RAAS sistema može biti korisna u kontroli DDB27. S druge strane, bolesnici sa DM i hipertenzijom imaju manji rizik od progresije DDB kada je albuminurija normalna (< 30 mg/g [3 mg/mmol] kreatinina), a primena antihipertenzivnih lekova (uključujući inhibitore RAAS, blokatore kalcijskih kanala, diuretike) ima za cilj da smanji rizik od kardiovaskularnih komplikacija kod ove grupe bolesnika28.

Ispitivanja sprovedena kod bolesnika u ranom stadiju DM1 ili DM2 pokazala su da intenzivna kontrola glukoze u krvni rano u toku bolesti smanjuje rizik od razvoja DDB u kasnijem dužem vremenskom periodu praćenja29. Ovaj „efekt nasleđa“, nazvan i „metaboličko pamćenje“, sugeriše da intenzivna kontrola glikemije u ranoj fazi može sprečiti irreversible oštećenja povezana sa hiperglikemijom29. Kod bolesnika sa DM1, u poredenju sa bolesnicima sa hemoglobinom A1c (HbA1c) većim od 7%, stroga kontrola glikemije sa HbA1c manjim od 7% smanjuje rizik od razvoja mikroalbuminuirije za 34% i makroalbuminuirije za 56% tokom devet godina praćenja29. Nakon 22 godine praćenja, grupa intenzivne terapije i stroge kontrole glikemije imala je oko 50% manji rizik od sniženja JGF ispod 60 ml/min/1,73 m2, a prosečni gubitak JGF je značajno bio manji: od 1,56 ml/min/1,73 m2 godišnje uz standardnu terapiju do 1,27 ml/min/1,73 m2 godišnje uz intenzivnu terapiju30.

Slično, kod bolesnika sa novodijagnostikovanim DM2, intenzivna kontrola glikemije sa HbA1c do 7% tokom 10 godina dovela je do smanjenja razvoja mikroalbuminuirije uz uključujući DDB za 24% u poredenju sa bolesnicima sa HbA1c iznad 7%. Posle 12 godina, intenzivna kontrola glikemije rezultovala je smanjenjem rizika od 33% za razvoj mikroproteinuirije ili patoloških proteinuirija, i značajnog smanjenja broja bolesnika koji su imali dva puta viši kreatinin u serumu u odnosu na početnu vrednost u odnosu na grupu bolesnika sa konvencionalnom terapijom (0,9% : 3,5%)31.

Lečenje bolesnika sa bolesti bubrega i dijabetesom

Bolesnike sa dijabetesom i HBB treba lečiti sveobuhvatno, primenom strategije za smanjenje rizika od napredovanja bolesti bubrega i kardiovaskularnih bolesti. Plan lečenja, tj. promena načina života i primena hipoglikemika kod bolesnika sa DM2 i HBB prikazan je u Algoritmu 1.

Numerous studies showed the simultaneous presence of hypertension and DKD, with albuminuria, significantly raises the risk of diabetic microvascular complications and the development of DKD25,26. Even in normotensive patients with DM2 and albuminuria, the use of RAAS blockers may be useful in controlling DKD27. On the other hand, patients withDM and hypertension have a lower risk of DKD progression when albuminuria is normal (< 30 mg/g [3 mg/mmol] of creatinine), and use of antihypertensive drugs (including RAAS inhibitors, calcium channel blockers, diuretics) aims to lower the risk of cardiovascular complications in this group of patients28.

The research conducted on patients in the early stages of DM1 or DM2 showed that intensive glycemic control, early in the disease, lowers the risk of DKD development in later longer follow-up period28. This „hereditary effect“, also called „metabolic memory“, suggests intensive glycemic control in the early stage may prevent irreversible damage connected to hyperglycemia28. In patients with DM1, when compared to patients with hemoglobin A1c (HbA1c) higher than 7%, strict glycemic control with HbA1c below 7% lowers the risk of microalbuminuria by 34% and macroalbuminuria by 56% during a nine-year follow-up period29. After 22 years of follow-up, the group with intensive therapy and strict glycemic control had about a 50% lower risk of reduction of GFR below 60 ml/min/1,73 m2, and an average loss of GFR was significantly lower: from 1,56 ml/min/1,73 m2 a year, with standard therapy to 1,27 ml/min/1,73 m2 a year, with intensive therapy30.

Similarly, in patients with newly diagnosed DM2, intensive glycemic control with HbA1c up to 7% during 10 year period led to a reduction of the development of microvascular complications, including DKD by 24% compared to patients with HbA1c above 7%. After 12 years, intensive glycemic control resulted in lowering the risk of microproteinuria or pathologic proteinuria by 33%, and a significant reduction in the number of patients who had twice as high creatinine serum levels compared to starter levels when compared to the group of patients with conventional therapy (0,9% : 3,5%)31.
**Algorithm 1. Glicemic control in patients with diabetes mellitus type 2 and chronic kidney disease**

### a) Diet and lifestyle

Patients with DKD are advised to eat food rich in vegetables, fruits, wholegrain cereals, fibers, legumes, plant proteins, unsaturated fats, nuts, less processed meat, and refined carbohydrates. It is suggested to keep protein intake at 0.8 g of protein/kg of body weight /day for those with DM and CKD who are not dialyzed. The intake of sodium should be less than 2 g a day (or < 90 mmol of sodium = < 5 g of sodium chloride a day).

These patients are advised physical activity of moderate intensity, for at least 150 minutes a week or up to the level agreeable with their cardiovascular system and physical tolerance. It’s recommended to quit smoking.

### b) Blood pressure control and use of RAAS blockers

Recommendations from KDIGO guidelines, from 2020, suggest starting therapy with angiotensin converting enzyme inhibitors, which can retard the progression of diabetic kidney disease.
enzym inhibitors (ACEi) or angiotensin II receptor blockers (ARB) in patients with DM, hypertension and albuminuria. The doses should be titrated slowly, up until the highest tolerated dose (Algorithm 2). The combination of these drugs at the same time is not recommended because it didn’t enhance their efficacy, and what’s more, when combined they can be harmful. Besides blood pressure monitoring, changes in creatinine and potassium serum levels should be followed in further 2-4 weeks after starting or increasing ACEi or ARB doses (Algorithm 2). If the serum levels of creatinine rise more than 30% from the starting value in the following four weeks these drugs should be discontinued. Another precaution tied to the use of ACEi or ARBs is hyperkalemia which can be treated by taking measures that will reduce potassium levels instead of lowering or discontinuing these drugs.

Algorithm 2. RAAS treatment-dose adjustment and monitoring in patients with diabetic kidney disease

RAAS inhibitors have a double favorable effect on kidneys – they lead to albuminuria regression and reduce kidney function deterioration independently of their influence on blood pressure. Their favorable effects come from their ability to lower intraglomerular pressure in DKD. Targeted blood pressure values in DKD patients, in different stages of CKD, depending on the diabetes type and patient’s age are shown in Table 2.
**Tabela 2.** Ciljni pritisak kod bolesnika sa dijabetesnom bolesti bubrega u različitim stadijumima funkcije bubrega

| Normalna JGF i albuminurija/ Normal GFR and albuminuria | Normalna JGF i mikroalbuminurija/ Normal GFR and microalbuminuria | HBB stadijum 1−3/ CKD stages 1−3 | HBB stadijum 4−5/ CKD stages 4−5 | HBB stadijum 5D/ CKD stage 5D |
|---------------------------------------------------------|--------------------------------------------------------------|---------------------------------|---------------------------------|-----------------------------|
| DM1 < 140/80−90 < 130/80 za < 30 god./ years of age       | ≤ 130/80 < 120/80                                             | ≤ 140/90 ≤ 130/80 sa mikroalbuminurijom/ with microalbuminuria | ≤ 140/90 interdijalizni/ interdialysis |
| DM2 < 140/90 < 150/90 za ≥ 75 god./ years of age         | < 130/80                                                     | < 140/90                         | < 140/90 interdijalizni/ interdialysis |

HBB - hronična bolest bubrega, stadijum 5D - dijaliza/ CKD - Chronic kidney disease, stage 5D - dialysis

**c) Glikoregulacija**

Za praćenje i kontrolu glikemije, vodič preporučuje merenje HbA1c kod bolesnika sa DM i HBB. Treba uzeti u obzir da tačnost i preciznost vrednosti HbA1c je manja kod osoba sa JGF ispod 30 ml/min/1,73 m², a zbog kraćeg poluživota eritrocita ili korišćenja stimulatora eritropeze za lečenje anemie kod bolesnika sa HBB u stadijum 4−5 i onih lečenih dijalizom.

Drugi način kontrole je kontinuirano praćenje glikemije, što je korisna metoda za bolesnike kod kojih HbA1c ne korisno je direktne izmerenih glikemija. Pored toga, kontinuirano praćenje glikemije omogućava bolesniku da sam kontroliše i kratkoročno titrira lekove, prevenira hipo- i hiper-glikemije i poboljšava kontrolu glikemije. Prednost kontinuiranog praćenja glikemije je posebno važna zbog rizika od hipoglikemije kod bolesnika sa HBB i DM kojima je propisano korišćenje insulinoterapije i sulfonylurea. Zbog rizika od hipoglikemije, preporučuje se HbA1c cilj od manje od 6,5% do 8,0% kod bolesnika sa DM i HBB.

**c) Glycemic control**

For glycemic follow-up and control, the guidelines recommend measuring Hba1c in patients with DM and CKD. It should be taken into account that the accuracy of HbA1c values is lower in persons with GFR below 30 ml/min/1,73 m², and due to the shorter half-life of the erythrocytes or use of erythropoiesis stimulators for anemia treatment in patients with CKD stages 4−5 and those who are dialysed.

The other way of control is a continuous glycemic follow-up, which is a useful method in patients in whom HbA1c doesn’t correlate directly with glycemia readings. Besides, continuous glycemia follow-up enables the patient to control and titrate short-term drug use, prevents hypoglycemia, and improves glycemic control. Glycemic follow-up is especially important because of the risk of hypoglycemia in those using insulin and sulfonylureas (prolonged drug half-life in CKD, gluconeogenesis disorder, weight loss, diet).

Individual target Hba1c is recommended, ranging from < 6,5% to < 8,0% in patients with DM and CKD who are not dialysed. The factors that should be taken care of in patients with DM and CKD are shown in Scheme 2. Stricter criteria, such as HbA1C 6,5% are applied to patients with shorter diabetes duration, younger age, with no complications, and longer life expectancy. In patients with hypoglycemia risk, recommended target Hba1c is 7,0%.
Pored ili umesto HbA1c za neke bolesnike može se koristiti i kontinuirano praćenje glikemije u opsegu 3,9–10,0 mmol/l[17].

Preporuka je započeti lečenje većine bolesnika sa DM, HBB sa eGFR ≥ 30 ml/min/1,73 m² primenom lekova prve linije (Algoritam 1): Metformin je jeftin i generalno dobro podnošljiv lek koji efikasno snižava glukozu u krvi ili SGLT2i, koji značajno smanjuje rizike od HBB i kardiovaskularnih bolesti. Kada ovi lekovi nisu dostupni ili se ne podnose ili kada su nedovoljni za postizanje individualizovanih vrednosti glikemije, treba izabrati dodatne lekove na osnovu želja pacijenata, komorbiditeta, JGF i troškova. Međutim, Metformin se izlučuje putem bubrega, pa sa smanjenjem funkcije bubrega se akumulira u organizmu čime se povećava rizik od laktične acidoze[8].

**Shema 2. Faktori koji određuju vrednost HbA1c kod bolesnika sa DM i HBB**

**Shema 2. Factors guiding decisions on individual glycated hemoglobin (HbA1c) targets in patients with DM and CKD**

Besides or instead of HbA1c, for some patients, continuous glycemic follow-up may be used as well, ranging from 3,9–10,0 mmol/l[17].

It’s recommended to start the treatment of the majority of patients with DM, CKD with eGFR ≥ 30 ml/min/1,73 m² by using the first-line drugs (Algorithm 1): Metformin is cheap and generally well tolerated; it effectively lowers blood glucose or SGLT2i, which significantly lower the risk of CKD and cardiovascular diseases. When these drugs aren’t available or are poorly tolerated, or are not enough for reaching individual glycemic targets, we should use additional drugs based on the patient’s wishes, comorbidities, GFR, and costs. However, Metformin is excreted via kidneys, so with kidney function change Metformin is accumulated in the body thus raising the risk of lactate acidosis[8].

**d) Lekovi koji uposravaju progresiju bolesti bubrega i kardiovaskularne bolesti zbog dijabetesa**

Preporuka KDIGO vodiča je da većinu bolesnika sa DM2 i DBB treba lečiti primenom inhibitora natrijum-glukoznog kotransportera (Sodium-Glucose Cotransporter 2 Inhibitor - SGLT2 (Algoritam 1))8, SGLT2 nisu samo antihyperglycemski lekovi, već imaju zaštitni uticaj na bubrežni i srčani rad kod bolesnika sa DM2 i HBB18. Tokom prvih nedeelta primene SGLT2 inhibitora može se uočiti prolazno i umereno pogoršanje JGF, ali je ono reverzibilno. Svoje dejstvo na bubrege SGLT2 ispoljavaju nezavisno od kontrole glikemije. Blokirajući kotransporter (u proksimalnim tubulima nefrona), oni smanjuju reabsorpciju natrijuma, koja je povećana.

**d) The drugs slowing down the progression of kidney and cardiovascular disease because of diabetes**

The recommendation of the KDIGO guidelines, for the majority of patients with DM2 and DKD, is that they should be treated with Sodium-Glucose Cotransporter 2 Inhibitor - SGLT2 (Algorithm 1). SGLT2s are not only antihyperglycemic drugs but they also have a protective effect on kidney and heart function in patients with DM2 and CKD18. During the first weeks of SGLT2 inhibitor use, a transient and moderate deterioration of GFR may be noticed but it’s reversible. The influence of SGLT2 on kidneys is irrespective of their glycemic control. Blocking the co-transporter (in the proximal nephron tubule), they reduce the reabsorption of sodium,
kod bolesnika sa DM zbog višeg tubularnog opterećenja glukoze. Dobijena natriureza smanjuje intravaskularni volumen i krvni pritisak. Istovremeno, povećanje natrijuma u urinu na nivou macula densa normalizuje tubulo-glomerularnu povratnu spregu, dovodi do konstrkicije prethodno proširene aferentne arteriole i na taj način smanjuje intraglomerularni pritisak i glomerularnu hiperfiltraciju. Smanjenje glomerularne hiperfiltracije može, hipotetički, da uspori brzinu napredovanja bolesti bubrega.

U mnogim studijama dokazano je da je SGLT2 usporavajući progresiju HBB kod bolesnika sa DBB sa različitim stepenom smanjenja JGF i različitom albuminurijom. Iako je smanjenje relativnog rizika od bubrežne insuficijencije slično kod bolesnika sa normalnom i povećanom albuminurijom, smanjenje apsolutnog rizika je veće kod bolesnika sa albuminurijom ≥ 300 mg/dan. Ne samo da usporavaju progresiju DBB, već smanjuju rizik od kardiovaskularnih bolesti uključujući srčanu insuficijenciju kod ovih bolesnika.

U početku se smatrao da uvođenje SGLT2 treba izbegavati kod bolesnika sa JGF < 25 do 30 ml/min/1,73 m², jer se njihov hipoglikemijski efekat smanjuje s smanjenjem JGF. Odredna, prema odobrenju Federalne agencije za lekove - FDA, može se nastaviti kod bolesnika čija JGF na kraju padne ispod 25 ml/min/1,73 m² do započinjanja dijalize ili posle transplantacije bubrega. SGLT2 mogu da se kombinuju sa blokatorima RAAS, ali ne bi trebalo da se kombiniraju sa diuretikima, a posebno kod osoba koje već imaju hipovolemiiju. Ove lekove treba primenjivati sa oprezom kod bolesnika sa prethodnom amputacijom donjih ekstremiteta ili rizikom za amputaciju (npr. ulceracija donjih ekstremiteta i bolest periodnih arterija).

Inkretni. Bolesnici sa DM2 i DBB koji nisu postigli kontrolu glikemije upkos početnoj terapiji za snižavanje glukoze (Metformin i inhibitor SGLT2), primena inkretna - agonista receptora za protein sličan glukagonom (Glucagon-Like Peptide-1 Receptor Agonists - GLP-1) ili inhibitora dipeptidil peptidaze 4 (DPP4) može poboljšati kontrolu glikemije (Algoritam 1).

GLP1 je peptidni hormon koji proizvode enteroendokrine L čelije u zidu terminalnog i deca beleg veličina. Bezbroj stimulusa dovodi do oslobađanja GLP1 uključujući hranljive materije, neuroendokrine faktore, proizvode metabolizma bakterija i imunosistem, i citokin iz imunskih čelija, a prisustvo monosaharida u crevima, uključujući gluкоzu, galaktoku, fruktoku i metil-a-glukopiranoid, stimulisti postprimedijalno povećanje GLP1. To ima za posledicu stimulaciju lučenja insulina iz β-čelija pankreasa nakon unos-a sa ugljenih hidrata, supresiju lučenja glukagona iz α čelija pankreasa, usporavanje pražnjenja želuca i izazivanja sitosti putem direktnog delovanja u centralnom nervnom sistem. Svoje dejstvo GLP1 ispoljava vezujući se za specifične receptore, koji se nalaze u pankreasu, plućima, jetri, želuca, a unutar bubrega nađeni su u ćelijama endotela, proksimalnih

which is increased in patients with DM due to higher tubular glucose load. Obtained sodium diuresis lowers intravascular volume and blood pressure. At the same time, the increase of sodium in the urine, on the macula densa level, normalizes tubuloglomerular feedback, leads to constriction of previously dilated afferent arterioles, and thus lowers the intraglomerular pressure and glomerular hyperfiltration. The lowering of glomerular hyperfiltration may, hypothetically, slow down the speed of kidney disease progression.

Many studies proved that SGLT2s slow down CKD progression in patients with DKD and different levels of GFR, and varying albuminuria. Although the decrease of relative risk reduction of kidney disease is similar in patients with normal and increased albuminuria, the reduction of the absolute risk is higher in patients with albuminuria ≥ 300 mg/day. They not only slow down the progression of DKD but also reduce the risk of cardiovascular diseases, including heart failure in all patients.

In the beginning, it was believed that introduction of SGLT2s should be avoided in patients with GFR ≤ 25 to 30 ml/min/1,73 m² because their hypoglycemic effect is lower than the reduction of GFR. Recently, Food and Drug Administration FDA approved them also for those whose GFR drops below 25 ml/min/1,73 m² up until dialysis start or after the kidney transplant. SGLT2s may be combined with RAAS blockers but not with diuretics, especially in persons who are already hypovolemic. These drugs should be used with caution in patients with previous lower extremity amputation or the risk of amputation (i.e. Lower extremity ulcerations and periphery artery disease).

Incretins. Patients with DM2 and DKD, who didn’t accomplish proper glycemic control, despite the initial glucose-lowering therapy (Metformin and SGLT2 inhibitor), the use of incretins - glucagon-like peptide-1 receptor agonists - GLP-1 or inhibitors of dipeptidyl peptidase 4 - DPP4 may improve glycemic control (Algorithm 1).

GLP1 is a peptide hormone produced by enteroendocrine L cells in the terminal ileum and colon wall. Numerous stimuli lead to GLP1 release, including nutrients, neuroendocrine factors, bacteria metabolic products, immune system, and cytokines from immune cells. The presence of monosaccharides in the intestines, including glucose, galactose, fructose, and methyl-a-glucopyranose, stimulates the postprandial increase of GLP1. This results in stimulating insulin excretion from the pancreatic β-cells, after the carbohydrate intake, suppression of gluconic excretion from pancreatic α-cells, slowing down the stomach evacuation, and causing the feeling of satiety by directly affecting the central nervous system. GLP1 agonists act by binding to specific receptors in the pancreas, lungs, liver, stomach, inside the kidney, and they are found in the endothelial cells, proximal tubule, and juxtaglomerular cells. In healthy people, incretin release is responsible for almost 50–70% of insulin secretion, as a re-
Mineralocorticoid receptor antagonists. Mineralocorticoid receptor antagonists are found in collecting nephron tubules, but in colon, myocardium, and blood vessels as well. Their basic activity is the control of water excretion and sodium-potassium exchange, but an increased activity alleviates inflammation and tissue fibrosis, so therefore they are part of the kidney and cardiovascular disease development. On the other hand, Mineralocorticoid Receptor Antagonists - MRAs show renoprotective effects, and decrease albuminuria, and blood pressure in patients with CKD. Besides RAAS, they are used in heart failure treatment. In later meta-analyses it was proved that these steroid MRAs are effective in decreasing proteinuria in patients who were already treated with RAAS blockade. Despite this potential benefit for the kidneys, they are insufficiently used in CKD patients due to hyperkalemia, especially in those with already low GFR.

In recent years, selective, non-steroidal MRAs have been introduced. They bind only MRs, but not steroid receptors, so they haven’t got antiandrogenic or progesterone side effects. Current studies with Finerenone and Esaxerenone use in patients with DKD and different CKD stages and different MRAs have shown promising results in reducing albuminuria and improving kidney function.

It turned out the GLP1s have numerous protective effects on kidneys, including inhibition of inflammatory influences of angiotensin II, inhibition of oxidative stress, and albuminuria, as well as the ability to alleviate albuminuria, glomerular hyperfiltration, glomerular hypertrophy, and expansion of mesangial matrix in animal models. Similarly, GLP1 agonists lower the risk of progression of albuminuria to macroalbuminuria and potentially slow down GFR reduction in patients with DM2. Furthermore, numerous long-acting GLP1 agonists lower the risk of cardiovascular events in patients with DM2.

DPP4 inhibitors are oral hypoglycemics preventing the inactivation of GLP1 by inhibiting the DPP4 enzyme, therefore increasing the concentration of endogenous GLP1. Thus, DPP4 inhibitors indirectly stimulate insulin excretion, depending on glucose, and lower glucagon excretion from pancreatic α-cells by increasing the level of endogenous GLP1. Compared to GLP1 agonists, DPP4 inhibitors have milder effects on stomach emptying and weight loss. DPP4 inhibitors haven’t got a clear influence on the kidney function outcomes, although, they decrease the occurrence or deterioration of existing albuminuria.

**Antagonists of mineralocorticoid receptors:** Mineralocorticoid receptor antagonists are found in collecting nephron tubules, but in colon, myocardium, and blood vessels as well. Their basic activity is the control of water excretion and sodium-potassium exchange, but an increased activity alleviates inflammation and tissue fibrosis, so therefore they are part of the kidney and cardiovascular disease development. On the other hand, Mineralocorticoid Receptor Antagonists - MRAs show renoprotective effects, and decrease albuminuria, and blood pressure in patients with CKD. Besides RAAS, they are used in heart failure treatment. In later meta-analyses it was proved that these steroid MRAs are effective in decreasing proteinuria in patients who were already treated with RAAS blockade. Despite this potential benefit for the kidneys, they are insufficiently used in CKD patients due to hyperkalemia, especially in those with already low GFR.

In recent years, selective, non-steroidal MRAs have been introduced. They bind only MRs, but not steroid receptors, so they haven’t got antiandrogenic or progesterone side effects. Current studies with Finerenone and Esaxerenone use in patients with DKD and different CKD stages and differ
nerenona and Esakserenona for patients with DBB at different GFR stages and albuminuria categories, and a full dose of ACEi or ARBs, show that these MRAs decrease progressive damage of kidney function (measured as a double increase in serum creatinine and development of terminal kidney disease), decrease albuminuria, and the frequency of cardiovascular events (death due to heart disease reasons, myocardial infarction, stroke, or hospitalization due to heart failure) in patients with DM2 and DKD, and they affect blood pressure less\(^4\). Therefore, the addition of non-steroid selective MRA inhibitors is recommended (especially Finerenone), where available, and if potassium serum levels are lower or equal to 4.8 mmol/l, alongside ACEi or ARBs. Side effects include hyperkalemia, possible hypotension, and hyponatremia.

### Conclusion

Considering the fast-growing health issue of an increase in the number of patients with CKD, as a part of DM, we reviewed the guidelines for its treatment, published in 2020. The treatment of patients with DKD evolved during the last five years, with the emphasis on the long-term protection of the heart and kidney function. The research on SGLT2s, GLP-1 RAs, and finally non-steroidal MRAs point out their significant advantages in slowing down the progression of CKD and cardiovascular diseases. However, continuous work is needed to establish the influence of the combination of classic and novel therapy on the endpoints – heart and kidneys in DM patients.
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