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Some specificities in the management of hyperglycemia in patients with diabetic kidney disease

Neke specifičnosti glikemijske kontrole kod dijabetičara sa dijabetesnom bolesti bubrega

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Introduction

Chronic kidney disease (CKD) is a common condition that is estimated to affect over 50 million people worldwide [1]. Similarly, diabetes takes on epidemic proportions with global prevalence estimates of 382 million people [2]. According to American data, in approximately 45% of incident renal replacement treatment patients, diabetes is the primary cause of their kidney failure. People with CKD due to diabetes have significantly higher incidence of cardiovascular morbidity and mortality compared to diabetics without nephropathy, and it is eighty times higher than in the general population [3].

CKD resulted from diabetes has been termed "diabetic nephropathy" (DN). The Diabetes and Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney disease Outcomes Quality Initiative (NKF KDOQI) in its Clinical Practice Guidelines and Clinical Practice Recommendatione from 2007 has suggested that a diagnosis of CKD as a consequence of diabetes should be reffered to as diabetic kidney disease (DKD). The term diabetic nephropathy should be reserved for kidney disease attributed to diabetes with hystopathological injury demonstrated by renal biopsy [4]. The clinical diagnosis of DKD is primarily based on detection of albuminuria (proteinuria). Microalbuminuria is the term defined as an albumin/creatinine (A/C) ratio of 30–299 mg/g from a spot urine collection, or 30–299 mg/daily in the 24-hour urine collection. Macroalbuminuria is the term, defined as more than 300 mg/g or more than 300 mg/daily in the same tests respectively [5]. The incidence of DN is estimated to be 20–40% in both type 1 and type 2 diabetes. The natural history of DN in type 1 diabetes, typically shows a period of hyperfiltration followed by microalbuminuria (30–299 mg/day) and than by macroalbuminuria (>300 mg/day), accompanied by a decline in glomerular filtration rate (GFR). A similar progression is though to underline the natural course of nephropathy in type 2 diabetes, but other comorbidities, including hypertension or obesity, make a progressive pattern less clear [6].

Microalbuminuria in type 1 diabetes appears to be associated with typical histopathologycal lesions and confers risk for progression of CKD. In contrast to type 1 diabetic patients, the association between DKD and microalbuminuria is not as strong in patients with type 2 diabetes, and only 30% of them demonstrates the typical findings by kidney biopsy. However, if retinopathy is present in patients with type 2 diabetes and microalbuminuria, this is strongly suggestive of DKD, with a sensitivity of 100% and specificity of 46–62% [7]. About 30–40% of these patients remain within microabuminuric interval, and do not progress to higher degree of albumunuria over 5–10 years of follow up. The rest of them will progress to more significant levels of albumunuria, and are likely to progress to the end stage renal disease [8]. For the purpose of emphasizing the continuous nature of albuminuria as a risk factor, according to American Diabetes Association (ADA) recommendations, previous terms microalbuminuria and macroalbuminuria, will be rather reffered to as increased albumin excretion at levels more than 30 mg/daily [9].

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Some studies show that in patients with type 1 diabetes and persistent albuminuria in the range of 30–299 mg/g, screening for albuminuria alone would miss 20% of progressive disease [10]. Serum creatinine with estimated GFR should therefore be assesed at least annually in all adults with diabetes, regardless of the degree of albuminuria. In summary, in patients with diabetes who have persistently high urinary albumin excretion rate (persistent albuminuria) in combination with diabetic retinopathy, kidney disease may be atributed to diabetes and the severity of kidney impairment should be clasiffied depending on the GFR [1].

Intensive blood glycemic control

Glycemic control is fundamental to diabetes management. Chronically uncontrolled hyperglycemia leads to a higher risk of macrovascular and microvascular complications, such as cardiovascular disease, nephropathy, neuropathy, and retinopathy. In large prospective randomized studies, intensive diabetes management with the goal of achieving near-normoglycemia wih HbA1c levels of less than 7%, has been shown to reduce the risk for the appearance of microalbuminuria and delay its progression, in both types of diabetes. The Diabetes Control and Complications Trial (DCCT), a prospective randomised control study of intensive *versus* standard glycemic control, in patients with recently diagnosed type 1 diabetes, showed that intensive therapy significantly reduced the onset of microalbuminuria, after the mean of 6.5 years [11]. Further 16-year follow-up of the DCCT cohort patients demonstrated a long-term persistence of these microvascular benefits in previously intensively treated patients [12]. United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto trial, showed similar benefits of strict glycemic control on the developement of microalbuminuria in type 2 diabetic patients [13, 14].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VAD) studies, have added some new information to the evidence that even more intensive glycemic control reduces the onset and progression of elevated urinary albumun excretion in type 2 diabetic patients with long term diabetes and cardiovascular comorbidites [15–17]. However, comparison of the effects of different levels of the glycemic control in ACCORD trial was stopped early due to an increased all-cause mortality rate in the intensive compared to standard group, without reduction in frequency of major adverse cardiovascular disease (CVD) events, including CVD mortality and non-fatal CVD events. Although the initial analysis of the ACCORD data did not identify a clear explanation for the elevated mortality rate in the intensive treated group, severe hypoglicemia was significantly more frequently observed in patients randomised to the intensive glycemic control arm [15].

Considering all of the above, actual recommendations of the ADA suggest that the HbA1c values below or around 7% are a reasonable goal for most of the diabetic adults. For selected individuals with short diabetes duration, long life expectancy and no cardiovascular comorbidities, more strict HbA1c goal of less than 6.5% are suggested. For patients with long diabetes duration, limited life expectancy, advanced micro- and macrovascular complications and with history of severe hypoglycemia, less strict glycemic control, with the maintenance of HbA1c values below 8% are recommended [9]. Similar recommendations are proposed by the European Association for the Study of Diabetes (EASD) [18]. The American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) Global Guidelines suggest that HbA1c values have to be less than 6.5% for most of the patients, with the exception of the risk population for which HbA1c levels higher than 6.5% could be tolerated [2, 19].

Nevertheless, none of these organisationes has the separate guidelines for patients with diabetes kidney disease; still they all recognise that certain populations may require special considerations and that less intensive glycemic goals must be indicated in patients with severe or frequent hypoglycemia. In 1997, the National Kidney Foundation established the Kidney Disease Outcomes Quality Initiative (KDOQI) to develope clinical practice guidelines for management of all stages of CKD [4]. This guidelines is consistent with that of ADA, and actually recommend a target HbA1c of approximatelly 7% to prevent or delay progression of albuminuria in DKD. This guidelines also suggest that target HbA1c sholud be raised from 7% to 8% in individuals with clinically significant comorbidities, and a risk of hypoglycemia including patients with DKD [9, 18]. Interesting to note, in some [20, 21], but not all observational studies [22], HbA1c values between 7% and 9% were associated with better outcomes for survival, hospitalization and CVD in patients receiving hemodialysis. However, this observation has not been tested and proven in prospective randomised studies, so it cannot be included in the official recommendations yet.

Assessment of long term glycemic control

Glycated hemoglobin (HbA1c) is well-validated test for assessing glycemic control in general diabetic population. It is well-known that neither peritoneal nor hemodialysis acutely change HbA1c levels [23]. However, in patients with decreased kidney function, especially those on hemodialysis, factors such as reduced erytrocyte life span or iron deficiency, recent transfusions, metabolic acidosis and erythropoiesis stimulating agents (ESA) administration, affect the accuracy of this assay. By increasing the proportion of youth erytrocyte forms in blood, anemia can falsely lower HbA1c levels. Namely, the rate of glycation of these young cells is lower than that of old cells, which also contributes to the reduction in measured HbA1c levels. Once treatment with iron supplementation is started, HbA1c levels decreases significantly, as a result of the production of immature cells. Iron supplementation or erythropoietin administration, lead to the modest decrease of HbA1c level of 0.5% to 0.7% along with the rise in total hemoglobin in patients with advanced CKD [24]. On the other hand, iron deficiency increases the level of HbA1c independently on other factors. Each of these parameters increases the

possibility of underestimation of true glycemic control by HbA1c level in the presence of CKD (stages 3–5), making it unreliable for the assessment of glycemic control in the hemodialysis setting [25].

Measurement of glycated albumin (GA) has been shown to provide a more relevant method in assessing glycemic control in diabetic patients with chronic kidney failure. In the study on hemodialysis patients with diabetes, it was observed that the degree with which serum GA correlates with plasma glycemia was identical between diabetics with and without CKD [26]. Similarly to fructosamine, GA provides short term index of glycemic control that is not affected by erythrocyte lifespan or erythropoietine administration. This assay has the strong correlation with glucose and provides a reliable index of glycemic control over the proceeding 2–3 weeks. The evidence from the current literature indicates that in the presence of advanced CKD, glycemic control could be evaluated more trustworthy by measuring GA than HbA1c. Furthermore, it is observed that elevated values of GA are better marker than HbA1c in predicting the developement of vascular complications, cardiovascular death and hospitalization in dialysis diabetic patients [27].

There are also limitations of GA assay. Albumin turnover change in patients receiving peritoneal dialysis and in patients with macroproteinuria, in whom values of this assay, theoretically could be falsely lower as a result of a shorter glycemic exposure of plasma albumin [26]. Consequently, some autors recommend that the use of GA levels might be limited to patients on hemodialysis. Wheather glycated albumin could be a marker of the qualtity of glycemic control in patients with massive proteinuria, and in those undergoing peritoneal dialysis is still unclear. At present, there is still no consensus on discriminative values of this assay, which makes different target values for different stages of CKD highly needed. Until then, according to current recommendations, HbA1c remains the best clinical marker of long-term glycemic control in patients with DKD, particularly if combined with self-monitoring of blood glucose level [1].

Pathogenesis and risk for hypoglycemia in patients with CKD

Patients with decreased kidney function (CKD stages 3–5) have increased risk for hypoglicaemia, due to impaired gluconeogenesis in kidney, and decreased clearance of insulin and some oral hypoglicemic agents. In humans, only the liver and the kidney contain significant amounts of the enzyme glucose-6-phosphatase, and therefore are the only organs that are able to perform gluconeogenesis. As the result of differences in the distribution of various enzymes along the nephron, glucose utilization is occurring predominantly in the renal medulla, while glucose release is limited to the renal cortex. Like the brain, renal medullary cells are obligate users of glucose, but they can phosphorylate and accumulate glycogen. These cells, however lack gluconeogenic enzymes, and hence are not able to release free glucose into circulation. On the other hand, renal cortex cells do possess gluconeogenic enzymes (including glucose-6-phosphatase), and therefore can generate and release glucose into the blood stream [28]. After an overnight fast, 75–80% of glucose released into the circulation derives from the liver, and the remaining 20–25% derives from the kidneys.

In healthy subjects, hypoglycemia promotes three-fold increase of renal glucose release, while hepatic glucose release increased only 1.4-fold above ordinary rates, suggesting the important role of kidneys in human glucose counterregulation. With the reduction of cortical mass in DKD, a reduction in glucose delivery appears, thus contributing to higher hypoglicemic risk. Patients with type 1 diabetes and long term type 2 diabetes, lose their glucagon response to hypoglycemia and become dependent on catecholamine response. Consequently, type 1 diabetic patients with both reduced glucagon and epinephrine responses have decreased both hepatic and renal glucose release during hypoglycemia [29].

The kidney is the main organ responsible for metabolizing exogenous insulin administered to diabetic patients. About 65% of systemic insulin that reaches the kidney is filtered at the level of glomerulus, and is subsequently metabolized in the proximal tubular cells; furthermore it is eliminated via the peritubular endothelium and less than 1% of filtered insulin appears in the urine [16]. As renal failure progresses, peritubular insulin uptake increases. Until GFR decreases to less than 20 mL/min, this compensates for the decline in degradation of filtered insulin and afterwards half-life of insulin increases, due to its reduced clearance [30].

Insulin treatment-dose adjustment

The reduction of insulin clearance and catabolism leads to increased frequency of severe hypoglycemia, especially in patients with insulin dose not adequately modified. The reduction in insulin requirements seem to be similar for both type 1 and type 2 diabetic patients. In patients with type 1 diabetes mellitus and mean GFR of 54 ml/min some authors have observed that clearance of regular human insulin is reduced by 30–40% [31, 32]. Patients with residual diuresis less than 500 mL/day show a reduced demand for insulin by oboout 29%. It has been reported than one year after initiation of hemodialytic procedure, approximately one third of insulin threated type 2 diabetics didn't need insulin therapy at all [33]. A logical consequence of this observation is the reduction in insulin dose requirements. For patients with GFR >50 mL/min/1.73 m^2, no dose adjustment is required. For those with GFR values between 50–10 mL/min/1.73 m^2, it is recommended to decrease daily insulin doses by 25%, and even by 50% when GFR is less than 10 mL/min/1.73 m^2 [2, 4, 34].

Similar modifications applies to administration of insuline analogues. In patients with GFR reduction of less than 60 mL/min, the mean dose of insulin lispro should be reduced for aproximately 30% [33]. In contrast, patients with diabetes treated with insulin aspart do not show any singinificant change in the insulin dosage in relation to the renal filtration rate [35]. Recent studies show that type 1 diabetics with GFR less than 60 mL/min/1.73 m^2 requires daily dose reduction of insulin glargine by 32% and insulin detemir by 26% [33, 36].

Although current guidelines recommend maintaining of normoglycemia by implementing intensive treatment in diabetics with CKD, the potential benefits of this modality must be balanced against risk of hypoglycemia. Some authors recommend avoiding intermediate and long-acting insulin preparations in patients with CKD, while others advocate for their use. Individual approach when using combination of intermediate-acting and regular insulins or similarly acting analogues, seems to be the most acceptable for the achievement of satisfactory assessing glycemic control in this population [4].

Oral antidiabetic agents-dose adjustment

In contrast to scarce information concerning insulin treatment modifications in DKD, phamacological properties of oral antidiabetic agents and non-insulin injectables in chronic kidney failure, are rather well characterised throughout current literature.

Renal clearance of metformin is approximately 3.5-fold greater than creatinine clearance (CrCl), which indicates that tubular secretion is the major way of metformin elimination. After oral administration, approximately 90% of the absorbed medication is eliminated through the kidneys within the first 24 h, with the plasma half-life of approximately 6 h. In patients with decreased renal function based on measured CrCl, the plasma half-life of metformin is extended. Therefore, metformin should be avoided in patients with moderate to severe CKD. This refers to those on dialysis since the risk of metformin accumulation and lactic acidosis increases in line with the degree of reduction in GFR [37, 38].

The evidence suggests that metformin can be safely used in patients with plasma creatinine level less than 132 mmol/L. Since serum creatinine level may overestimate renal function, it is recommended to assess GFR. The clearance of metformin decreases by about 75% when the GFR is less than 60 mL/min/1.73 m^2 without any additional changes until the GFR reduction reaches value of 30 mL/min/1.73 m^2. With this value of the renal impairment, serum levels of metformin is only about two-fold higher than with normal kidney function, and these levels are still only about 3% of those found in patients with true metformin-associated lactic acidosis [39]. According to this, the use of metformin in moderate CKD disease is still controversial. Most of authors agree that the use of metformin should be avoided in patients with CKD stages 3–5 and with other risk factors that increase the possibility for lactic acidosis (congestive heart failure, chronic obstructive lung disease and liver disease) [38]. In patients without these risk factors, they suggest that metformin may be safely used without dose adjustment in CKD stages 3A and with half-dose reduction in stage 3B. For instance, the United States Food and Drug Administration (FDA) indicates that the use of metformin is forbidden for males with serum creatinine level equal or above 132 mmol/L and for female with serum creatinine level equal or higher than 124 mmo/L [18]. Other authors claim that the restriction of metformin use based on creatinine cutoffs provided by FDA, or a GFR cutoff of less than 60 ml/min is questionable, based on its clear clinical benefit [40]. This advice was adopted by current United Kingdom guidelines, as well as the Japanese Society of Nephrology, allowing metformin use until GFR drops below 30 mL/min/1.73 m^2 with the caution and dose reduction recommended at its level of 45 mL/min [18, 41].

First generation sulfonylureas are strictly forbidden in patients with CKD [1]. Glipizide is rapidly absorbed, reaching peak concentrations after 1.5 hours and is eliminated primarily by hepatic biotransformation. Approximately 90% of absorbed glipizide is excreted as biotransformation products in urine and feces, while less than 10% of a dose is excreted without any change [38, 39]. Glipizide is therefore a preffered oral anti-diabetic agent as it does not have active metabolites and does not increase the risk of hypoglycemia in patients with CKD stages 3–5 [1]. Gliclazide is extensively metabolised into various inactive metabolites and mainly excreted by the urine. Chronic kidney failure has little effect on the pharmacokinetic profile of this drug, and does not require dose adjustment for GFR from 30 to 60 mL/min [42]. After oral administration and absorbtion, glimepiride undergoes extensive hepatic metabolism to the inactive M2 metabolite, with the elimination half-life of 5-8 hours. Glimepiride clearance tends to increase in patients with CKD as GFR decreases, the terminal half-life is unaffected. Since the urinary clearance of its metabolites decreases with decreasing creatinine clearance, this drug can be used in patients with chronic kidney failure stages 3 and 4 with dose adjustment to the maximum of 1 mg daily [42, 43].

Glibenclamid should be avoided in patients with moderate to severe CKD (GFR less than 60 mL/min/1.73 m^2 [1].

The two available representative of thiazolidinediones (rosiglitazone and pioglitazone) are extensively metabolized by the liver. Rosiglitazone is mainly metabolized into inactive metabolites and less than 1% of the given drug dose appears in the urine in unchanged form. The half-life of rosiglitazone is similar in patients with end stage renal disease and in healthy individuals [44]. The same applies to pioglitazone. Its pharmacokinetic profile is similar in patients with normal renal function and CKD, as well as in those undergoing dialysis treatment [45]. These two drugs might also improve uremia-associated insulin resistance. So, this class of drugs can be administered without dose adjustment to patients with CKD stages 3 to 5, including those receiving dialysis. Potential side effects of peroxisome-proliferator-activated receptor-gamma (PPAR-gamma) treatment include fluid retention, hemodilution, bone loss and weight gain. Therefore, glitazones must be used with caution as they can increase fluid retention and deteriorate congestive heart fauilure, in the same as they can worsen underlying bone disease (renal osteodystrophy) [1].

Acarbose is the alfa-glucosidase inhibitor. This drug is only minimally absorbed after oral administration, but with the progression of kidney failure, serum level of acarbose and its metabolites increase significantly. In patients with severe renal failure and creatinine clearance less than 25 mL/min, the serum level of this drug become 5-fold higher than in healthy controls [38]. Therefore, American giudelines recommend that alfa-glucosidase inhibitors, including acar-

bose and miglitol, should be avoided in patients with GFR less than 25 mL/min/1.73 m^2 (or serum creatinine levels above 176 mmol/L) [44]. Despite this, Japanese autors recommend administration of acarbose without dose adjustment even in the dialysis population [46].

Exenatide and liraglutide are injectable incretine mimetics. Incretins, such as human glucagone-like peptid-1 (GLP-1), are hormones that are produced by the intestine and secreted into the blood stream, after food ingestion. On the other hand, the dipeptidyl-peptidase (DPP-4) inhibitors, such as sitagliptin, saxagliptin and linagliptin, decrease the degradation of GLP-1 and improve post-prandial glucose level. The kidney provides the main route for elimination and degradation of exenatide. In patients with modetare renal failure and CrCl more than 30 mL/min exenatide exposure was similar to healthy controls [47]. In subjects on dialysis, mean exenatide exposure increases 3.4 fold compared to subjects with normal kidney function. Therefore, according to the US guidelines, exenatide is not recommended for use in patients with a GFR less than 30 mL/min/1,73 m^2 [1].

The metabolism of liraglutide is similar to that of other large peptides, and there is no indications that the kidney is the major organ for its elimination. However, according to KDOQI recommendations, use of liraglutide should be avoided in patients with GFR less than 60 mL/min/1,73 m^2 [1].

Sitagliptin is primarily eliminated by the kidney *via* active secretion and glomerular filtration with approximately 80% of the oral dose excreted unchanged in the urine. As a consequence of this, it is recommended to adjust oral dose of sitagliptin for CKD stage 3 (50 mg daily) and stage 4 and 5 (25 mg daily). In contrast to other DPP-4 inhibitors, the major metabolite of saxtagliptin, is also pharmacologicaly active, but with only half of original potency. This drug is cleared by both hepatic metabolism and renal excretion. Therefore it is recommended to estimate the kidney function before starting saxagliptin therapy [38, 39]. Renal excretion is a minor elimination pathway of linagliptin at therapeutic dose level; therefore, a dose adjustment in subject with CKD is not required for this drug [38].

SGLT2 inhibitors are novel glucose-lowering agents that have been approved for the treatment of adults with type 2 diabetes. These drugs decreases reabsorption of filtered glucose in the renal tubule, and increases urinary glucose excretion with a consequent lowering of its plasma levels. The associated reduction in blood pressure may be related to adverse events of these drugs including urinary tract infections, osmotic diureasis and volume depletion. SGLT2 inhibition has been associated with modest, transient decrease in GFR, ranging from 3% to 10% that attenuated with continued treatment, and are consistent with volume loss associated with the osmotic diuresis [48]. Therefore, with progression of renal failure the treatment with SGLT2 becomes gradually ineffective. Canagliflozin therapy should not be started in patients with end-stage renal disease, on dialysis, or in those patients with GFR less than 60mL/min/1.73m^2. In canagliflozin-treated patients whose GFR falls below 60 ml/min/1.72 m^2 dose should be adjusted to 100 mg once daily [49]. In patients with moderate renal impairment, use of dapagliflozin was associated with increased incidence of renal-related adverse events [50]. Although renal function does not seem to be affected, the use of dapagliflozin in subjects with moderate to severe CKD (CrCl less than 60 mL/min) is not recommended [39].

Conclusion

Measurement of HbA1c remains the best clinical marker of long-term glycemic control in patients with diabetes and CKD. Glycated albumin might be more useful for assesment of glycemic control in patients with advanced stages of DKD. A HbA1c target value associated with the best outcome in predialysis and dialysis diabetics has not been established so far. According to recent longitudinal clinical trials, intensified glycemic control in diabetics with CKD leads to a substantial increase in severe and non-severe hypoglycemia, without reduction in the risk of major adverse cardiovascular disease events. Therefore it is recommended that the target HbA1c values for patients with long-standing diabetes and comorbidities including those with CKD, should be raised from 7% to 8%. Maintaining good glycemic control in the presence of reduced kidney function is complicated by altered glucose and insulin homeostasis. Decreased renal gluconeogenesis accompanied with a reduction in clearance of insulin and certain oral hypoglycemic agents, leads to an increased risk of hypoglicemia. Therefore, kidney function of each patient should be monitored and meticulously assessed. Oral antidiabetic drug selection, insulin dosage or the choice of insulin regimen type, as well as the maintenance of the best possible glycemic control must be individualy modified, taking into account that potential benefits must be balanced against potential risks.

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