An eBook on Diabetes

Chapter 3

Management of Diabetic Kidney Disease

Ander Vergara[1]; Clara García-Carro[1]; Irene Agraz[1]; Natalia Ramos[1]; Maria A. Azancot[1]; María José Soler[1]*

[1]Nephrology department, Hospital Universitari Vall d'Hebron. Nephrology research group, Vall d'Hebron Institut de Recerca (VHIR), Barcelona. Red de Investigaciones Renales (RedInRen). GEENDIAB.

***Correspondence to: María José Soler,** Nephrology department, Hospital Universitari Vall d'Hebron. Nephrology research group, Vall d'hebrón Institut de Recerca (VHIR), Barcelona. Red de Investigaciones Renales (RedInRen). GEENDIAB.*

Email: mjsoler01@gmail.com

1. Introduction

The global burden of diabetes is increasing around the world. Diabetic kidney disease (DKD), one of the microangiopathies secondary to diabetes, will occur in 30–40% of people with diabetes, and one-third of these individuals may develop kidney failure. Currently, DKD is the first cause of end-stage kidney disease (ESKD) worldwide [1]. Thus, DKD treatment and management should be one of the first cornerstone to prevent its progression. Classical studies demonstrated that DKD progression may be delayed by a multidisciplinary approach that included blood pressure lowering, glucose control, and smoking cessation among others. [2]. By targeting the multiple modifiable cardiovascular risk factors, the STENO group demonstrated that the annual decline in glomerular filtration rate (GFR) was significantly lower, mortality greatly reduced as compared as the previous cohort from the group, indicating that the multifactorial treatment leaded to better risk factor management and improved prognosis for patients with type 2 diabetes suffering from DKD [2].

Several randomized clinical trials studies have been performed in DKD patients. However, until 2016 only renin angiotensin system (RAS) blockade has clearly demonstrated to delay DKD progression [3,4]. Recently, new antidiabetic agents namely sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide receptor agonists (GLP-1 RAs). have shown cardio protective effects in diabetic patients and/or renoprotective effects in patients with diabetes [3,4]. After the significant discoveries in the last 10 years, in this chapter book we will focus in the classical and new strategies in the DKD management. In addition,

blood sugar treatment and hemoglobin glycated goal, blood pressure recommendations and goals in the blood pressure targets, and lipid lowering strategies in DKD will also be addressed in the current chapter.

2. Classical Strategies in the DKD Management

Chronic kidney disease (CKD) is a common complication in patients with diabetes mellitus (DM) and further contributes to increased mortality and cardiovascular disease. The prevalence of CKD defined as an estimated glomerular filtration rate (eGFR)<60mL/min/1.73m2 and/or the presence of microalbuminuria in adults with type 2 diabetes mellitus (T2DM) was 45% and raised to 61% in patients >65 years according to the NHANES report [5]. As previously mentioned, DKD is the most common cause of end-stage renal disease in Western Societies, accounting for approximately 45% of patients on renal replacement therapy [6].

The first clinical sign suggesting renal involvement secondary to diabetes is hyperfiltration characterized by increased glomerular filtration rate over 120 mL/min/1.73 m2, which is followed by the onset of microalbuminuria (urinary albumin to creatinine ratio 30-300 mg/g). However, the natural history of diabetic nephropathy is not well established in T2DM since alterations of glucose metabolism are indolent and the diagnosis of diabetes is usually performed many years later .Without specific intervention, from 20% to 40% of T2DM patients with microalbuminuria are going to progress to macroalbuminuria (urinary albumin to creatinine ratio >300 mg/g). 20 years after the beginning of macroalbuminuria, around 20 percent of patients will progress to ESKD [7].

Classical studies with small groups of patients provided contradictory results between changes in albuminuria and kidney disease progression. In the Action to Control cardiovascular Risk in Diabetes (ACCORD) trial in people with long-duration type 2 diabetes, intensive glycemic control resulted in significantly fewer individuals developing albuminuria at moderately increased levels (30-300mg/g creatinine) or severely increased levels (>300mg/g creatinine) but increased the risk of doubling of serum creatinine [8]. Activation of the renin-angiotensin-system aldosterone (RAAS) is a key component in progression of chronic disease, mainly in the presence of albuminuria and diabetes [9]. Renin angiotensin system blockade, either by angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptors blockade (ARB), is decisive in the reduction of proteinuria and in the slowing of renal disease. ACEi or ARB treatment have demonstrated to slow down the progression of kidney disease in hypertensive patients with diabetes with an eGFR less than 60mL/min/1.73 m2 and a urine albumin–creatinine ratio greater than 300mg/g [10,11].

The NKF-KDOQI™ Guidelines on Hypertension and antihypertensive Agents in CKD recommended a version of the DASH (Dietary Approaches to Stop Hypertension) diet with

modifications for patients with CKD at stages 3 and 4. These modifications decreased dietary protein from 1.4 g/kg body weight per day to 0.6 to 0.8 g/kg body weight per day, as well as restricted phosphorus (0.8 to 1.0 g/d) and potassium (2 to 4 g/d). In CKD stages 1 to 2, the Work Group concluded that a protein intake that meets, but does not exceed, the recommended diet allowance would be prudent at earlier stages of CKD [12]. The ADA (American Diabetes Association) endorses a dietary protein intake of 0.8 g/kg body weight per day for people with DKD. An additional restriction to 0.6g/kg body weight per day is suggested when glomerular filtration rate begin to decrease [7].

3. New Strategies in the DKD Management

Despite improve in clinical management, diabetic patients present similar risk of ESRD in 2010 as compared to 1990 [13]. Until 2016, RAS blockade has been the only treatment that demonstrated a delay in progression of DKD [11]. Recently, SGLT2i have shown a cardio protective effect in diabetic patients and a renoprotective effect in all stages of DKD [14–17]. In addition, Glucagon-like peptide-1 receptor agonist (GLP-1 RAs) have also demonstrated a beneficial effect in terms of cardiovascular risk and albuminuria [18,19]. Thus, SGLT2i and GLP-1 RAs constitute a new paradigm in the treatment of patients with DKD.

SGLT2i promote urinary excretion of glucose by blocking SGLT2 receptor in the proximal tubule and inhibiting glucose reabsorption. Blood glucose levels decrease without modification in insulin sensitivity, what implies a lower rate of hypoglycemia [20]. These agents are shown to reduce glycated hemoglobin (HbA1c) by 0.6-%-1.2% [21]. Moreover, SGLT2i enhances natriuresis promoting a diuretic effect. Majo randomized clinical trials have recently shown that SGLT2i are effective in cardiovascular prevention and renal protection in patients with type 2 diabetes. EMPAREG study showed a decrease in death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke in patients with established cardiovascular disease and eGFR≥30mL/min/1.73m2 receiving empagliflozin as compared with placebo on top of the standard of care [22]. Patients on empagliflozin group presented a decrease in body weight, waist circumference, uric acid level and blood pressure. In patients with DKD, treatment with empagliflozin demonstrated benefits in terms of worsening nephropathy and progression from micro to macro albuminuria, as well as a lower rate of renal replace therapy initiation. Empagliflozin was associated with an eGFR decrease within the first weeks of treatment. At the end of follow up, SLGT2i group presented a stable eGFR versus a decrease in the placebo group [23]. These results, suggest that the decrease in GFR at the empagliflozin initiation is associated with an hemodynamic effect that may act in part as a protector against GFR delay at the end of the study after long-term SGLT2i therapy.

Canagliflozin and dapagliflozin cardiovascular effects were studied in the Canvas Program and in DECLARE TIMI 58 randomized clinical trials respectively [15,24]. The

Canvas Program included type 2 diabetic patients with history of cardiovascular disease, two or more major cardiovascular risk factors and eGFR≥30mL/min/1.73m2 while patients included in DECLARE TIMI 58 may have eGFR≥60mL/min/1.73m2. As well as empagliflozin, canagliflozin decreased HbA1c levels, blood pressure and body weight when compared with placebo. Deaths from cardiovascular cause, non-fatal myocardial infarction and non-fatal stroke were also decreased. Regarding renal outcomes, canagliflozin reduced the risk of progression of renal insufficiency, renal replacement therapy or death from renal causes. Moreover, canagliflozin reduces albuminuria progression and derived to albuminuria regression more frequently than placebo. As expected, dapagliflozin also decreased HbA1c levels, blood pressure and body weight, and patients in dapagliflozin group showed a lower rate of heart failure when compared with placebo. In addition, dapagliflozin also demonstrated renal benefits (reduction in progression of renal insufficiency, renal replacement therapy and death from renal cause) [17]. A seminal study published in 2019 has clearly demonstrated the renoprotective effect of SGLT2i in patients with advanced DKD [25]. Previously, SGLT2i use was limited to eGFR>45 mL/min/1.73m2. This new trial compared canagliflozin on top of RAS blockade to placebo in eGFR30-90mL/min/1.73m2 and urinary albumin-to-creatinine ratio 300-5000 mg/g. CREDENCE study demonstrated that Canagliflozin was safe in advanced CKD patients with diabetes, and decreased the risk of kidney failure, progression of renal insufficiency and cardiovascular events in this patients with DKD [25].

GLP-1RAs are GLP1-RAs are glucagon-like peptide 1 (GLP-1) analogues, a molecule that increases insulin secretion in response to food intake. GLP-1RAs improve HbA1c levels by 1%-1.5% and reduce body weight [18,26]. These new drugs, GLP-1RAs eliminate text fragment demonstrated to reduce major adverse cardiovascular events (MACEs) and decrease macro albuminuria [18, 26-28]. Liraglutide, semaglutide and albiglutide have demonstrated to reduce three-point MACEs in a 3.8 years, 2.1 years and 1.6 years of follow-up respectively [18,26,29]. Benefits of liraglutide were more evident in patients with established CKD (eGFR below 60mL/min/1.73m^2) and in patients with cardiovascular disease at baseline.

Regarding to the renoprotective effects, liraglutide was associated with reduced incidence of worsening nephropathy, mainly driven by a lower incidence of persistent macro albuminuria. There were no significant differences in doubling of serum creatinine, ESKD or death from renal causes [27]. Semaglutide showed similar results [26]. Interestingly, dulaglutide was able to reduce the decline in eGFR in patients with CKD G3 and G4 as compared with insulin glargine, both combined with insulin lispro [28]. This beneficial effect was more evident in patients with urine albumin-to-creatinine ratio higher than 300mg/g.

The positive effects of SLGT2i and GLP-1RAs used in combination are not very well established. The DURATION-8 trial reported a significant reduction in HbA1c, in body weight and in systolic blood pressure in type 2 diabetic patients on treatment with metformin who

were randomized to exenatide plus dapagliflozin, exenatide alone or dapagliflozin alone, all of them on top of metformin [30]. When dulaglutide was added to inadequately controlled diabetic patients receiving SLGT2i, HbA1c levels significantly improved but weight and SBP reduction was only observed with high dose of dulaglutide [31]. Similar benefits in terms of HbA1c levels reduction were observed when liraglutide was added to insulin degludec [32]. Of mention that the rates of adverse events of different combinations of SGLT2i and GLP-1RAs were similar to monotherapy.

These two new groups of antidiabetic agents, both SGLT2i and GLP-1RAs, are nowadays a second line treatment in patients with type 2 diabetes. The positive effects in terms of cardiovascular and renal protection make these drugs a new promising first line therapy for DKD in the near future.

4. Blood Sugar Treatment and Hemoglobin glycated goal in DKD

In type 1 and 2 diabetic patients, blood glucose reduction to almost normal values has proven to reduce microvascular (retinopathy and nephropathy) and cardiovascular (CV) events, especially during long-term treatments [33,34]. These protective effects are more evident and emerge earlier for renal and ocular complications than for CV events. The reductions are greater when improving poor glycemic control and more modest when trying to achieve near normal glucose values in patients who already have acceptable blood glucose control. Moreover, intensive glucose lowering therapies have an increased risk of immediate and short-term harms such as hypoglycemic events and weight gain. For these reasons, recent guidelines suggest personalizing glycemic targets based on patient characteristics, as well as adherence and treatment tolerance (**Table 1**) [35].

Table 1: Recommended glycemic targets for nonpregnant adults by different guidelines.

Parameter	American Diabetes Association (ADA)(37)	American Association of Clinical Endocrinologists (AACE)(38)	Kidney Disease Improving Global Outcomes (KDIGO) (67)	Kidney Disease Outcomes Quality Initiative (KDOQI) (68)
Hemoglobin A_{1c}	• <6.5% (48 mmol/mol) for selected patients that meet one or more of the following criteria: -Short duration of diabetes. -Long life expectancy. -No concurrent illness. -No significant microvascular or macrovascular complications. -Goal can be achieved without significant adverse effects or multiple drug rescription (polypharmacy). • <7.0% (53 mmol/mol) a reasonable goal for many	• ≤6.5% (48 mmol/mol) for most patients, especially if they meet the following criteria: -No concurrent serious illness. -Low hypoglycemic risk. • >6.5% (48 mmol/mol) when lower targets cannot be achieved without adverse events. Usually applicable	Recommendations are made for patients with known CKD: • ~7.0% (53 mmol/mol) is the recommended target to prevent or delay progression of microvascular complications. • <7.0% (53 mmol/mol) not recommended in patients at risk of hypoglycemia.	Recommendations are made for patients with known CKD: • ~7.0% (53 mmol/mol) is the recommended target to prevent or delay progression of microvascular complications. • <7.0% (53 mmol/mol) not recommended in patients at risk of hypoglycemia.

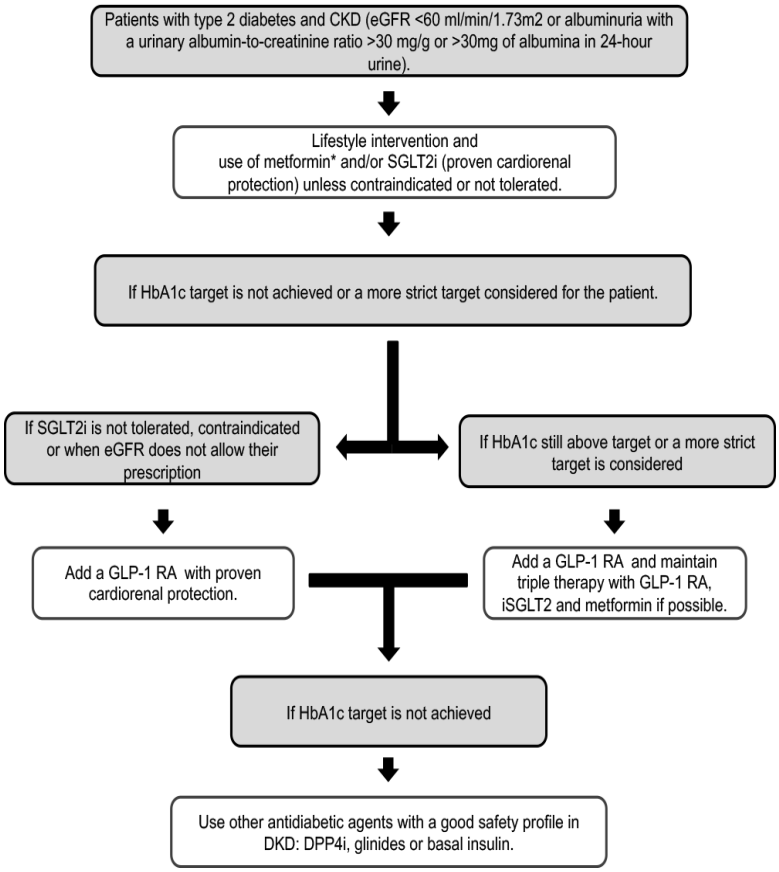
Hemoglobin A_{1c}	patients. • <8.0% (64 mmol/mol) for selected patients that meet one or more of the following criteria: -History of severe hypoglycemia. -Limited life expectancy. -Extensive comorbid conditions. -Advanced microvascular or macrovascular complications. -Long-standing diabetes in which haemoglobin A1c goals are difficult to achieve despite intensive efforts.	to patients that meet one or more of the following criteria: -Concurrent serious illness. -Hypoglycemic risk.	• HbA1c target could be extended above 7.0% (53 mmol/mol) in selected patients thath meet one or more of the following criteria: -Significant comorbidities. -Limited life expectancy. -Risk of hypoglycemia	• HbA1c target could be extended above 7.0% (53 mmol/mol) in selected patients thath meet one or more of the following criteria: -Significant comorbidities. -Limited life expectancy. -Risk of hypoglycemia.
Fasting lasma Glucose	80-130 mg/dL	<110 mg/dL		
2 hour postprandial glucose	<180 mg/dL	<140 mg/dL		

In patients with DKD, decrease of glomerular filtration rates drives to an accumulation of uremic toxins, chronic inflammation, metabolic acidosis or vitamin D deficiency. These alterations in body metabolism induce a proinflammatory state and increase insulin resistance [36]. In addition, a lower GFR reduces the clearance of many glucose-lowering medications, changing their safety profile and increasing the risk of adverse events, including hypoglycemia [36]. These features make patients with DKD a unique population with specific issues to consider before and during antidiabetic treatment.

Although recent guidelines have proposed a more flexible glycemic goals based on patients characteristics (**Figure 1**) [37,38], there are not many studies that evaluate the accuracy of (HbA1c) for glucose monitoring in patients with DKD and reduced GFR. Conditions that affect the red blood cell turnover can vary HbA1c levels, regardless of glycemic control. In DKD, as in other kidney diseases, there is an erythropoietin deficiency and a tendency to anemia which may reduce HbA1c levels, leading to underestimation of hyperglycemia [36]. In this sense, it is recommended to evaluate HbA1c values together with patient self-monitoring of blood glucose (SMBG) [37]. The few studies that analyzed the relation between HbA1c levels and clinical outcomes in patients with DKD demonstrated a U-shaped association where levels lower than 6-6.5% and higher than 9% of HbA1c were independently associated with increased mortality, which was mainly driven by CV disease [39,40]. The impact of HbA1c levels on end-stage renal disease (ESRD) development is less certain. The deleterious effect of tight glycemic control has been mainly related to the hypoglycemic adverse events ascribed to the classical blood glucose lowering agents and short-acting insulins. In this sense, the

new blood glucose lowering agents and long-acting insulins offer the possibility of decreasing HbA1c with less deleterious effects in terms of severe hypoglycemia.

Algorithm 1: Recommendations for hyperglycemia treatment in patients with type 2 diabetes and DKD.



DKD: diabetic kidney disease; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; SGLT2i: sodium-glucose co-transporter 2 inhibitor; GLP-1 RA: glucagon-like peptide-1 receptor agonist; DPP4i: dipeptidyl peptidase 4 inhibitor. *Remember to withdrawn metformin in patients with eGFR < 30mL/min/1.73m2)

When it comes to choosing an antidiabetic drug in patients with DKD, the recent CV outcomes trials are leading to a change in different guidelines. The CV safety studies required by the United States Food and Drug Administration (FDA) since 2008 for new antidiabetic drugs and the results of the latter, have changed the hemoglobinocentric perspective of diabetic treatment to an organ-targeted therapy. The patient's previous complications as well as the organo-specific protection the physicians want to achieve, will guide the selection of an antidiabetic treatment [41]. In this line, the protective effects of SGLT2i and GLP-1 RAs on cardiovascular outcomes, heart failure (HF) and DKD progression, have made these drugs a recommended second-line therapy. In the specific case of DKD, a multifactorial intervention to improve glycemic control, lower blood pressure (BP), manage elevated low density lipoprotein-cholesterol (LDL-c) levels, reduce weight or quit smoking is considered the best option [42]. Guidelines highlight the importance of helping patients understand their disease and assume daily control of diabetes. Lifestyle measures, such as weight loss and physical activity, are the first step in diabetes treatment and metformin is still considered the first-line drug in DKD if there is no contraindication [41,42]. When HbA1c goal cannot be achieved with metformin monotherapy or when physicians are seeking for a lower target in patients were

DKD predominates, SGLT2i are indicated for dual therapy in various consensus documents. However, if SGLT2i are not tolerated or decreased GFR does not allow their prescription, another option for patients with DKD is initiating GLP-1 RAs in combination with metformin (**see Figure 1**) [41,42].

5. Blood Pressure Recommendations and goals in DKD

High blood pressure (HBP) is a known strong risk factor for the development and progression of chronic kidney disease (CKD) and one of the major cardiovascular risk factors [43]. Around 70-80% patients with type 2 Diabetes Mellitus have HBP. Hypertension in patients with DM is about twice than in age-matched individuals without DM [44]. The last European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines recommend for most individuals with diabetes mellitus to achieve a blood pressure goal of 140/80 mmHg. Intensive blood pressure-lowering strategy to reduce systolic blood pressure under 130 mmHg may be considered for younger patients with high cardiovascular risk and albuminuria [45]. Surprisingly, the guidelines of American College of Cardiology/ American Heart Association (ACC/AHA) recommended therapeutic goal below 130/80 in all patients with hypertension (see **Table 2**) [46]. Leehey et al. in the study VA NEPHRON-D, observed that achieved tight BP goal was associated with less mortality and better renal survival [43]. However, different recent randomized clinical trials, ACCORD study and ADVANCE study, were not able to observe benefits with intensive treatment (BP<120/80) as compared to usual blood pressure goal (<140/90) [47,48]. In contrast, a later systematic review demonstrated that a reduction in systolic blood pressure (SBP) below 130 is associated with a lower risk of mortality, mainly associated with a lower risk of stroke and heart failure [49]. To achieve a SBP level lower than 130 is difficult and worsens with the aging. This may be related to the fact that older people have an increased arterial stiffness that may difficult to achieve this goal of treatment [50].

Table 2: Blood pressure target recommendations (ESH/ESC, ACC/AHA, ESC/EASD, ADA) in patients with diabetic kidney disease

	ESH/ESC-2018(46)	ACC/AHA-2018(69)	ESC/EASD-2019(45)	ADA-2019(44)
Therapeutic goal	SBP 120-140 DBP 70-80 * >65 years SBP 130-140	SBP/DBP<130/80	SBP 120-130 DBP 70-80 * >65 years SBP 130-140	SBP/DBP <140/90 *High CV risk factors <130-80
Recommended treatment	ARBs + CCBs/Thiazida/ thiazide-like diuretic	ACEI, ARBs, CCBs, diuretics * ARBs or ACEi if albuminuria	ARBs or ACEIs * ARBs or ACEIs + CCBs as first line	ARBs or ACEIs
Observations	ARBs + ACEi must be avoided		ARBs + ACEi must be avoided	ARBs + ACEi must be avoided

ESH/ESC: European Society of Hypertension/European Society of Cardiology; ACC/AHA: American College of Cardiology/ American Heart Association; ESC/EASD: European Society of Cardiology/ European Association for the Study of Diabetes; ADA: American Diabetes Association; SBP: Systolic Blood Pressure, DBP:Diastolic Blood Pressure, CV: Cardiovascular; ARBs: Angiotensin Receptors Blockers, ACEi: Angiotensin Converting Enzyme inhibitors, CCBs: Calcium channel blocker

Classical studies performed by Lewis and Brenner among others demonstrated that in patients with diabetes mellitus, high blood pressure, decrease glomerular filtration (< 60ml/min/1.73m2) and macroalbuminuria, RAS blockade either by ACEi or ARB exerts a reno protective effect and are first-line antihypertensive treatment in this group of patients [11,51,52]. In contrast, Bangalore S et al. in a metanalysis and systematic review found that the effect of RAS blockade was similar as any other antihypertensive therapy in diabetic patients without renal disease [53]. As no significant clinical differences exist between ACEi or ARBs, the use of one or another will depend on the preference of physicians and the patients susceptibility to specific adverse effects (hypotension, cough, angioedema) [54]. The renoprotective effect of RAS blockade (ACEi or ARB) on type 2 diabetes with normoalbuminuria is controversial, despite the BENEDICT study demonstrated that the use of trandolapril plus verapamil and trandolapril alone decreased the incidence of new onset microalbuminuria as compared to verapamil alone in type 2 DM [55]; Haller et al. were not able to demonstrate a positive effect of Olmesartan on the development of microalbuminuria in type 2 DM patients with normoalbuminuria [56]. The ONTARGET and VA NEPHRON-D studies, demonstrated that therapeutic combinations of ACEi and ARB in DKD patients should be avoided for increased adverse effects namely hypotension, syncope, hyperkalemia and renal dysfunction without significant clinical benefits [43,54]. Of mention that the European Society of Cardiology/ European Association for the Study of Diabetes guidelines recommended avoiding the use of beta blockers and diuretics in prediabetic patients because this combination favors the development of DM. In addition, the beneficial effects on managing HBP of the new lowering glucose therapies such as GLP1- receptor agonist and SGLT2i inhibitors should to be taken into consideration [45].

The use of mineralocorticoid receptor antagonist (eplerenone, spironolactone, or finerenone) is effective in the treatment of resistant hypertension. Different studies demonstrated that the combination of ACEi or ARB plus mineralocorticoid receptor antagonists leads further reduction of macroalbuminuria in DKD, however their use is limited for the risk of severe hyperkalemia [57]. A new nonsteroidal mineralocorticoid receptor antagonist, Finerenone, is currently being studied in two randomized clinical trials named FIDELIO and FINERENONA and seems a promising new good strategic option for patients with DKD. Finerenone is more than 500-fold selective over other mineralocorticoid receptors which made this drug especially suitable for minimizing secondary effects related to other corticoadrenal receptors. In preclinical studies, finerenone has demonstrated greater reductions in microalbuminuria than eplerenone with small increase in serum potassium levels. Despite the potential beneficial effects of finerenone in terms of cardiovascular and renal protection, large and long-time follow-up randomized clinical trials are currently ongoing to test their real clinical beneficial effect and safely use [57].

6. Lipid-lowering drugs in DKD

Cardiovascular disease (CVD) is the main cause of death and disability in patients with diabetes mellitus (DM). It is estimated that patients with DM have a twofold to threefold increased risk of cardiovascular events than patients without diabetes and, it is considered a coronary heart disease equivalent [58]. Dyslipidemia in the patient with diabetes, is an important factor for accelerated atherosclerosis. The phenotype of dyslipidemia in the patient with diabetes is characterized by an increase of triglycerides (TG), reduced high density lipoprotein (HDL-C), smaller low density lipoprotein (LDL-C), but similar levels of LDL-C compared with general population [59]. Thus, hypertriglyceridemia is the most common lipid abnormality in diabetic patients. The mechanisms of dyslipidemia in patients with diabetes are not totally understood. However it has been described that patients with insulin resistance and glucose intolerance have a compensatory increase in insulin levels, which stimulates secretion of very low density lipoproteins (VLDL-C) and TG by the liver. Moreover, there are overproductions of chylomicrons that are rich in TG and an impairment of lipoprotein lipase leads to decrease metabolism of chylomicrons and VLDL-C [60].

Different international guidelines focused on the target levels of lipids in patients with diabetes. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) and the 2004 update recommend treating dyslipidemia to LDL-C and non-HDL-C targets based on the risk for cardiovascular (CV) events in the next 10 years. In patients with diabetes without previous history of cardiovascular events, the LDL-C target is lower than 100 mg/dL (non-HDL-C level <130 mg/dL). In very high-risk patients, such as those with established coronary artery disease, a recent acute coronary syndrome or multiple poorly-controlled components of metabolic syndrome, the LDL-C goal is lower than 70 mg/dL (non-HDL-C level <100 mg/dL).

Recently, the new European Society of Cardiology (ESC) ESC Guidelines on diabetes, pre-diabetes, and cardiovascular disease developed in collaboration with EASD (European Association for the Study of Diabetes) have been published [4]. This guidelines recommend a target of LDL-C <100 mg/dL in patients with T2DM with moderate CV risk, a target of LDL-C <70 mg/dL and a LDL-C reduction of at least 50% in patients with T2DM and high CV risk, and LDL-C target of <55 mg/dL and LDL-C reduction of at least 50% in patients with T2DM at very high CV risk. In patients with T2DM, they also recommend a secondary goal of a non-HDL-C target <85 mg/dL in very high CV risk patients and <100 mg/dL in high CV risk patients [61].

Patients with DKD are considered very high CV risk patients. However, the relationship between CV risk and levels of LDL-C is lost as estimated glomerular filtration rate (eGFR) declines. KDIGO 2013 Clinical Practice Guideline for Lipid Management in Chronic Kidney

Disease recommends the use of lipid lowering drugs in patients with CKD not on dialysis and over 50 years. In patients < 50 years old, the indication of these drugs are limited for patients with known coronary disease, diabetics and previous stroke [62].

Statins or statin/ezetimibe are considered the first option to treat diabetic dyslipidemia, but the treatment in patients with DKD may be challenging. Patients with DKD are at high risk for medication-related adverse events, perhaps because of the reduced renal excretion, frequent polypharmacy and high prevalence of comorbidity. Therefore, KDIGO advises reducing the dose if eGFR is <60 ml/min/1.73m2, based on the reduced renal excretion of some statins for minimizing the risk of myopathy, rhabdomyolysis and hepatotoxicity [62]. This recommendation essentially means that high-intensity statin therapy should be avoided in patients with CKD. However, this point deserves an important revision. Atorvastatin does not need dose adjustment in patients with CKD and Rosuvastatin requires adjustment in patients with eGFR <30 ml/min/1.73m2. On the other hand, a recent post hoc analysis of 4D Study (Die Deutsche Diabetes Dialyze) concluded that Atorvastatin was able to reduce the risk of fatal and nonfatal cardiac events and death from any cause in T2DM patients on dialysis if pre-treatment LDL-cholesterol is >145 mg/dl (3.76 mmol/L) [63]. Taken together, KDIGO recommendations seem to be restrictive in use of statins especially in T2DM patients with end stage renal disease (ESRD).

Currently, very little evidence exists to recommend the use of fibrates in patients with CKD including DKD, unless triglyceride levels are very high (>11.3 mmol/l (>1,000 mg/dl)). In this case, fibrate therapy should be dose adjusted for renal function. KDIGO guidelines recommend therapeutic lifestyles changes in case of TG elevates in CKD [62].

Proprotein convertase subtilisin kexin 9(PCSK9) is a secreted serine protease that binds to the extracellular domain of the hepatocyte LDL-receptor and promotes its lysosomal degradation [64]. Monoclonal antibodies that act as PCSK9 inhibitors sequester PCSK9 and thereby prevent LDL receptor catabolism, leading to an increase in LDL receptor density on hepatocytes [65]. Different monoclonal antibodies such as alirocumab, evolocumab, and bococizumab are available and they are indicated in patients at very high CV risk, with persistent high LDL-C despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance [61]. There is scarce evidence of use of PCSK9 inhibitors in patients with DKD, but in a phase III ODYSSEY trial that included 467 with CKD stage 3 an efficacy and safety profile comparable to that of patients with normal renal function was observed [66].

Therefore, patients with DKD are considered very high CV risk patients, related in part to the presence of dyslipidemia. In patients with DKD, especially those with very low eGFR, treatment with lipid lowering drugs may be challenging, for the differences and uncertainties

in the current published guidelines, which make them restrictive in treatments. In this regard, it is clear the benefit of statin treatment on CV risk in patients with diabetes and eGFR >15 ml/min/1.73m2. Further studies are needed to assess the indication and safety of PSCK9 inhibitors in the diabetic population with chronic kidney disease.

In summary, the treatment of patients with diabetic kidney disease should be basde in a multidisciplinary approach that included blood pressure lowering, glucose control, lipid lowering therapy, exercise, healthy diet and smoking cessation among others. The multidisciplinary approach, classical RAS blockade and the new antidiabetic drugs with beneficial effects in terms of renal and cardio protection are the clue for offering the best strategic treatment in DKD. New therapeutic agents that target other altered pathways such as fibrosis, oxidative stress, and inflammation are currently in the pipeline.

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