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Quarterly Medical Review - Type 2 diabetes: Contemporary challenges

Renal disease in patients with type 2 diabetes: Magnitude of the problem, risk factors and preventive strategies

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1. Introduction

Diabetic kidney disease (DKD) is a serious diabetes-mediated chronic vascular complications and denotes a significant burden for both patients and society. DKD not only represents the major cause for end stage renal disease (ESRD) but is paralleled by an increase in cardiovascular morbidity and mortality.

Interventions to delay its development and its progression are the key approach for DKD and the associated cardiovascular burden.

Treatment for DKD lies both on optimal metabolic and haemodynamic control. Lifestyle measures have also an important role.

In the 1990s, with the introduction of drugs inhibiting the renin angiotensin aldosterone system (RAAS) and, more recently, the use of SGLT2 inhibitors, GLP1 agonists, and novel nonsteroidal selective mineralocorticoid receptor antagonist, have provided new tools for the battle against DKD.

New therapeutic approaches have the properties to significantly improved the outcome of DKD; in this review, we will discuss the current challenges of DKD in patients with diabetes and the state-of-the-art treatments we ought to implement to prevent this devastating chronic diabetic vascular complication.

2. Epidemiology of diabetes and diabetic kidney disease

The diabetes epidemic represents a huge problem worldwide [1]. Recent studies have estimated, for 2021, a global diabetes prevalence of 10.5% (536.6 million people) in individuals between 20 and 79 years old; this is expected to rise to 12.2% (783.2 million) in 2045.

Diabetes prevalence is similar in men and women, highest in the elderly and more prevalent in urban-high income, rather than in rural-low income, communities [1]. Global diabetes-related health expenditures have been estimated to be around 966 billion USD in 2021, a cost projected to increase to 1054 billion USD by 2045 [1].

Approximately one-third of the diabetic population will develop DKD.

Type 1 diabetes (T1DM) encompasses approximately 10% of the whole diabetes population; 30% of patients with T1DM will develop DKD usually not earlier than 10 years of diabetes duration despite this prevalence has been falling secondary to improvement in patient care.

In patients with type 2 diabetes (T2DM) the prevalence of DKD is similar, around 30–40% of patients. Patients with type 2 diabetes still represent an older group where parallel pathologies such as vascular disease are often present.

The epidemic of type 2 diabetes has resulted in diabetes being the most common cause of ESRD worldwide.

Data from the USA suggest that the ageing of populations, the increase in comorbid conditions, such as diabetes, obesity and hypertension, and the reduction in death rates because of improved treatments will result in increased prevalence of ESRD even if novel renoprotective treatments have been introduced [2].

This scenario will likely add more pressure to any health care system. Prevention of disease progression is key for DKD, and the search for novel therapeutic tools represents the key strategy to fight this disease.

3. Clinical presentation and risk factors

Diabetic kidney disease is a clinical diagnosis and its presentation can differ.

Typically we observe, in particular in patients with T1DM, an initial phase characterised by glomerular hyperfiltration, followed by albuminuria (microalbuminuria, and macroalbuminuria), hypertension, overt proteinuria, and progressive loss of glomerular filtration rate (GFR), that ultimately leads to ESRD [3,4]. 30–40% of patients will develop DKD. DKD is often paralleled by the presence of diabetic retinopathy.

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The renal glomerular anatomo-structural changes include an initial mesangial expansion and deposition of extracellular matrix, thickening of the glomerular basement membrane, and arterioles hyalinosis [5]. The severity of the glomerular lesions has been classified into four classes according to the magnitude of extracellular matrix deposition [6]. The typical glomerular lesions have been initially described by Kimmelstiel and Wilson, and are characterised by glomerular nodular fibrotic formations [7]. Other glomerular structural lesions are characterised by podocytes detachment (and loss in the urine), with denudation of the glomerular capillaries [8].

Glomerular lesions are also paralleled by tubulointerstitial lesions characterised by interstitial inflammatory infiltrates, tubular atrophy, and fibrosis [5,9].

Most patients with diabetes will present with classical features of DKD as described above.

The fall in GFR seen in DKD is often paralleled by albuminuria but at time patients remain normoalbuminuric [10,11], an event mainly observed in T2DM [12–14], and rarely seen in T1DM [15].

The lack of albuminuria often reflects a non-classical DKD which is associated with elevated cardiovascular morbidity and mortality [16], presence of diffuse renal tissue macroangiopathy with atherosclerotic vascular disease [17], often linked to hypertension, atherosclerotic diffuse vascular disease, and insulin resistance [18].

Further, individuals with T2DM can present with renal function decline but without signs of retinopathy and a history of good diabetes control; this often suggests non-diabetic renal disease often presenting with a mixture of diabetes-related and non-diabetes related histological lesions [19,20], and a renal biopsy is often required for diagnosis [21,22] (Fig. 1).

The heterogeneity of DKD in T2DM is reflected in a reduction of the prevalence of diabetic retinopathy (~50%) [23] and, in T2DM, DKD can even precede diabetic retinopathy [24].

Poor glycaemic control has been implicated in the pathophysiology of DKD and studies in T1DM have proven that better metabolic control improves renal outcomes in DKD [25]. Maintaining a good glycaemic control ameliorates hyperfiltration which some believe could represent a risk factor for renal function decline [26].

Glomerular hyperfiltration is clinically observed in patients with T1DM but rarely in T2DM [27]. In patients with T2DM we are often unable to define the time of the initial phases of DKD.

Investigators have proposed that glomerular hyperfiltration, as seen in diabetes, could represent an important factor for DKD progression [27,28] but this was not supported by all studies [29–32]. In more recent studies of relatively long duration, hyperfiltration was an independent risk factor for accelerated DKD progression despite good diabetes and blood pressure control [33].

Glomerular hyperfiltration reflects an increase in glomerular pressure and a haemodynamic insult to the glomerular structure, which leads to anatomo-structural damage. Even in the presence of normal systemic pressures, glomerular capillary hypertension synergizes with metabolic perturbations and contributed to the development and progression of DKD [34–36]. In advanced stages of DKD, where a reduction in functioning nephrons occurs, compensatory hyperfiltration of functioning nephrons could also contribute to disease progression [37].

Patients with diabetes of Afro-Caribbean origin are predisposed to hypertension and consequently to more progressive DKD [38,39]. These ethnic groups are characterised by higher salt sensitivity, with increased RAAS activity which results in glomerular hypertension [40]. Higher salt sensitivity [41,42] is often associated with insulin resistance [43–45] and both have been associated with a worse DKD outcome (albuminuria, and chronic loss of renal function) by predisposing toward hypertension [43].

Mechanisms of hyperfiltration reside in diabetes-mediated tubular hypertrophy, as seen in the initial stages of DKD, that are paralleled by an upregulation of SGLT2 with increased glucose and sodium reabsorption at the level of the proximal tubule that, by tubule-glomerular feedback, result in glomerular afferent arteriolae vasodilation [46–48]. Of interest studies conducted in T1DM patients with normoalbuminuria have described a correlation between glomerular hyperfiltration and proximal tubular reabsorption of sodium [49].

Further diabetes-mediated glomerular local activation of the RAAS results in increased angiotentin-2 production that by binding to its receptor [50,51], more abundantly expressed on the glomerular efferent arteriolae (compared to the afferent one), results in unbalanced vasoconstriction, efferent > afferent arteriolae and secondary glomerular hypertension [36]. Both these mechanisms lead to glomerular hypertension and haemodynamic perturbation to the glomerulus [36].

A genetic cause/predisposition has been proposed for DKD; yet, no clear major specific gene/s or epigenetic effect has been found [5,52,53].

The risk of development and progression of DKD lies mainly on poor glycaemic and blood pressure control and lifestyle aspects such as obesity, dyslipidaemia, lack of exercise, and smoking.

Obesity, mainly visceral obesity, is a recognised pattern seen in T2DM (metabolic syndrome) and is an important factor for DKD progression [54]. Visceral obesity is paralleled by RAAS activation [55,56]

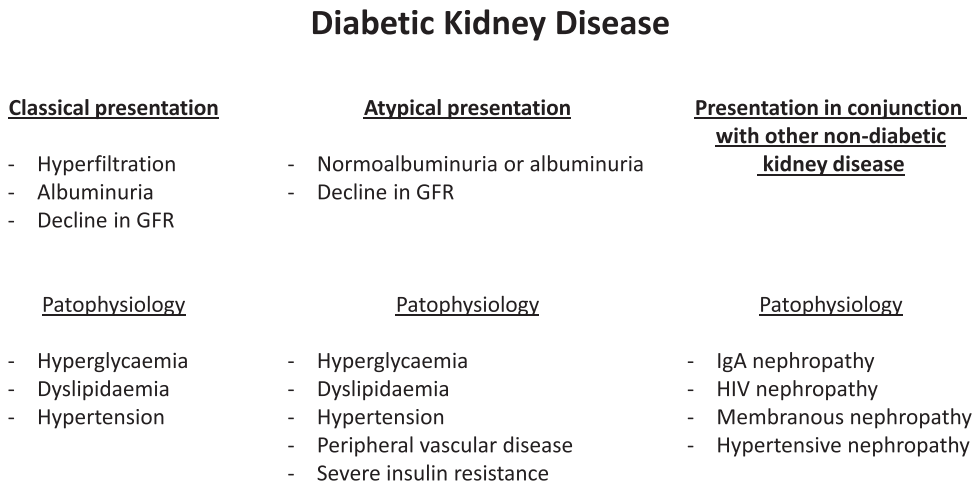

Fig. 1. Schematic representation of the clinical presentation and pathophysiology of diabetic kidney disease.

and, in humans, is paralleled by hyperfiltration that resolves with weight loss [57,58] in parallel with many other beneficial effects such as amelioration of insulin sensitivity, and risk factors such as lipid profile and blood pressure.

Patients with DKD are at high risk of cardiovascular disease and every patient should be offered treatment with a statin. Statins' use associates with reduction of albuminuria and rate of progression of DKD [59]; a statin-mediated anti-inflammatory, anti-oxidative, and anti-fibrotic mechanisms have been proposed [60–62].

Declining GFR and albuminuria are independently and additively associated with an increase in cardiovascular morbidity and mortality [63–65] which is 2–3 times higher than the one seen in patients with diabetes but without DKD [66].

Patients who reach dialysis are often the "protected ones" as most will die from cardiovascular disease before they start renal replacement therapy.

4. Preventive strategies

As said above the most effective approach to reduce DKD-mediate ESRD is to prevent and delay the renal function decline seen in patients with diabetes.

The achievement of good glycaemic/metabolic control is an important task. Prospective randomized controlled trials (DCCT-EDIC) in T1DM have shown that intensive treatment (22 years total duration) aimed at achieving a tighter glycaemic control resulted in a reduction of albuminuria and reduced loss of GFR [25,67]. Importantly, sustained good glycaemic control was shown to confer a "metabolic memory" and long-term beneficial renoprotective effects [25,67,68].

For patients with T2DM, at diagnosis, the UKPDS prospective study demonstrated that intensive glycaemic control reduced the risk for the development of albuminuria by about 33%, and significantly reduced the proportion of patients doubling their plasma creatinine over 12 years [69,70]. Similarly, a continued reduction in microvascular risk was observed during 10 years of UKPDS post-trial follow-up [71].

Other studies, conducted in patients with T2DM with approximately 10 years' duration of disease, poor glycaemic control (HbA1c ~ 9%), and high vascular risk did not show any benefit of intensive glycaemic control on micro- and macrovascular disease outcomes after an average follow-up of 4–6 years [72–74]. Only the ADVANCE trial found a positive effect of intensified metabolic control on nephropathy [75].

The overall failure of these trials on diabetic renal complications was likely the short duration of the studies; further, an excess risk of hypoglycaemia was observed in patients on intensified therapy, an event that becomes more prominent in patients with reduced renal function, being the kidney a gluconeogenetic organ involved in insulin clearance [76,77].

Control of blood pressure (haemodynamic perturbations) has shown beneficial effects on the progression of DKD [5]. Inhibitors of the RAAS, such as angiotensin-2 converting enzyme inhibitors (ACEis) and angiotensin-2 receptor blockers (ARBs) are currently the first-line treatment for patients with DKD (with or without albuminuria), as they have shown to reduce albuminuria and renal disease progression [5].

Combination therapy with ACEis/ARBs has been associated with an increased risk of acute kidney injury and hyperkalaemia. In the Nephron-D study [78], patients with T2DM, DKD and albuminuria, RAAS inhibition with either ARBs, or a combination of ARB and ACEI did not affect renal outcome but was associated with an increased risk of adverse events.

The use of ACEis or ARBs significantly reduces plasma aldosterone levels, however, in approximately 50% of patients' aldosterone levels can subsequently start to increase (driven by raising potassium levels) to pre-treatment levels or above [79,80]. An increase in aldosterone retains a synergistic effect on the angiotensin-2 mediated alteration in glomerular haemodynamics and evidences exist of aldosterone-mediated deleterious pro-inflammatory and pro-fibrotic effects on the glomeruli and tubular compartment, which can promote renal disease progression [81].

In clinical trials on patients with T2DM on ACEIs, ARBs, or combination treatment, the addition of aldosterone antagonists led to a 30–60% significant reduction in albuminuria compared to placebo [82]. Other studies showed that adding the mineralocorticoid antagonist spironolactone to ACEI or ARB therapy has a renoprotective effect [83,84].

Combination of an aldosterone antagonist with ACEIs or ARBs therapy can often result in an increase in plasma potassium. Patients, with conditions such as CKD stage 4–5 or heart failure, are at higher risk of hyperkalaemia [85].

As clinicians we should conduct a careful risk-benefit assessment for those patients whom we want to consider for double RAAS blockade [86].

Recently a nonsteroidal, selective mineralocorticoid receptor antagonist, finerenone, has shown a favourable side effects profile for hyperkalaemia in patients with DKD treated with ACEis or ARBs. Indeed, finerenone has been shown to confer cardiovascular and renal protection in patients with T2DM, CKD and albuminuria [87,88].

Despite the beneficial effects of finerenone in DKD, when used with other RAAS blockade agents, it was associated with hyperkalaemia. Conceivably, in the careful assessment and selection of our patients that could benefit from the cardiorenal protection conferred by mineralocorticoid receptor antagonists (when used within double RAAS blockade), hyperkalaemia remains an important side effect and, in selected patients, parallel use of potassium binders could be considered [89]. Patients with CKD stage 2–3 are likely to benefit more from the association of ACEis or ARBs with finerenone because of the reduced risk of hyperkalaemia.

SGLT2 inhibitors, used as oral hypoglycaemic agents, have been developed to counteract the SGLT2 upregulation in the S1 and S2 segments of the proximal tubule as seen in diabetes [47]. SGLT2 drives the reabsorption of glucose and sodium in the proximal tubule [90,91]. Blocking the action of SGLT2 with specific inhibitors results in improvement in glycaemic control (HbA1c reduction of approximately 1%), weight loss (3–5 Kgs body weight), and blood pressure lowering (approximately 3–5 mmHg).

In the last few years, clinical trials have demonstrated an important SGLT2 inhibitors-mediated reduction in cardiovascular morbidity and mortality mainly driven by a reduction in cardiovascular death and hospitalization for heart failure [92–94]. The EMPAREG trial also suggested a reno-protective role for the SGLT2 inhibitor empagliflozin [95] which was later confirmed by other studies such as the CANVAS and CANVAS-R study programme, that showed a promising renoprotective effect of the SGLT2 inhibitor canagliflozin [96]. More recently the CREDENCE trial has demonstrated a definitive SGLT2 inhibitor-mediated renoprotective effect with a 30% reduction of end-stage kidney disease (defined as initiation of dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes when compared to the placebo arm [97].

Of major interest, other studies have described the SGLT2 inhibitors-mediated renoprotective effects also in the non-diabetic population [98].

These observations have opened a lively debate on the potential mechanisms implicated in the cardio-renal protective effect of SGLT2 inhibitors. The cardio-renoprotective is likely driven by a haemodynamic effect and different mechanisms have been implicated: most attractive proposed mechanisms reside in an activation of the

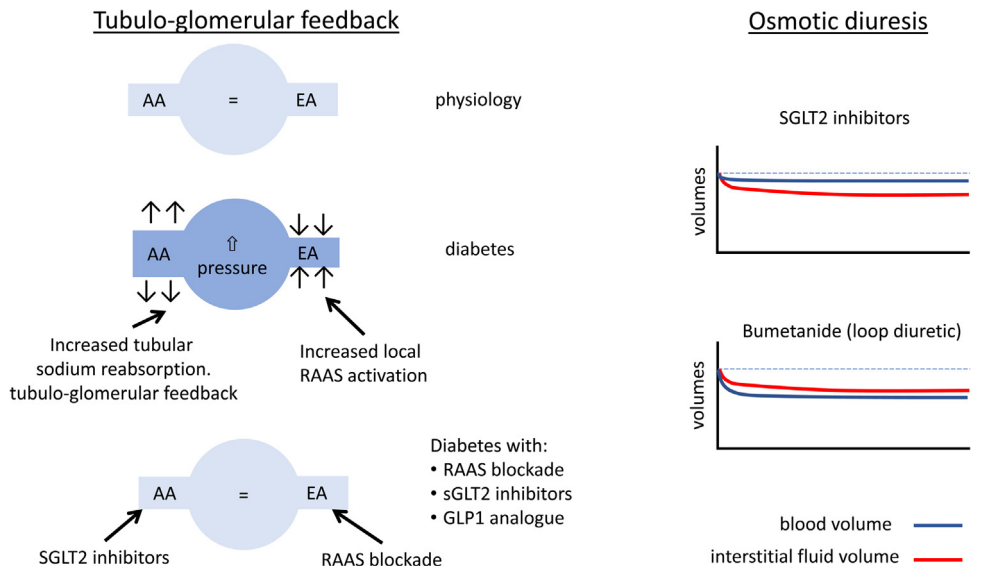

Fig. 2. SGLT2-mediated inhibition of sodium and glucose proximal tubule reabsorption (left) results in afferent glomerular arteriolae (AA) vasoconstriction by tubulo-glomerular feedback. In parallel, use of RAAS inhibition leads to efferent glomerular arteriolae (EA) vasodilation resulting in a normalisation of the increased glomerular pressure as seen in diabetes.

The osmotic diuresis mediated by SGLT2 inhibitors (right) results, when compared to a loop diuretic, in maintenance of circulating volume, possibly supporting better tissue circulation and oxygenation.

tubulo-glomerular feedback leading to a fall in glomerular capillary pressure [99], and the SGLT2 inhibitors-mediated osmotic diuresis which confers a congestion relief with minimal impact on circulating blood volume and organ perfusion [100] (Fig. 2). More studies are required to better dissect the mechanisms involved in the SGLT2 inhibitors'-mediated cardio-renal protection.

The incretin pathway has also been shown to confer renoprotection. Studies have suggested a renoprotective effect of GLP1 analogues [101]. In the AWARD-7 trial, T2DM patients with moderate-to-severe CKD treated with the GLP-1 analogue dulaglutide, benefited of a reduction in renal function decline when compared to the placebo arm [102]. As for SGLT2, the renoprotective mechanisms of GLP-1 agonists are unclear: in experimental animal models of diabetes, GLP1 receptor agonists have been shown to ameliorate renal inflammation and albuminuria [103], and to reduce proximal tubule sodium reabsorption and possibly inhibit angiotensin-2 expression [104,105].

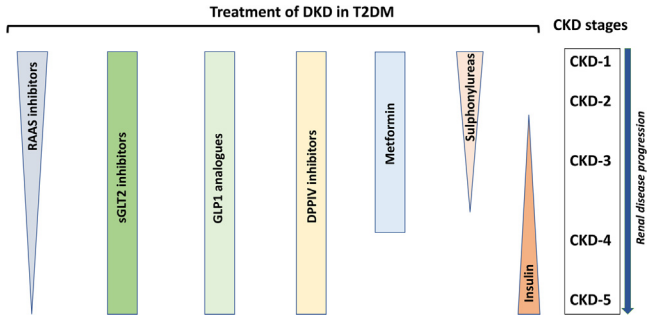

Fig. 3. Treatment of DKD in T2DM. In diabetes both sGLT2 inhibitors and GLP-1 analogues should be continued throughout the CKD stages (for both the hypoglycaemic and renoprotective effect). Use of sulphonylurea and metformin should be limited in CKD stages 1–3 because of risk of hypoglycaemia and reduced clearance for metformin (as renal function declines) respectively. Use of RAAS inhibitors (ACEis, ARBs, mineralcorticoid antagonists) should be implemented as soon as possible and only reduced with reduced renal function (CKD stages 4–5) because of rick of hyperkalaemia. Use of insulin, especially in CKD stages 4–5, should account for increased risk of hypoglycaemia in these patients.

5. Summary and conclusions

After the introduction of RAAS inhibitors in the 1990s, I believe we have been entering exciting new times with new effective medications (SGLT2 inhibitors, GLP-1 agonists, nonsteroidal mineralocorticoid receptor antagonist) to fight renal disease in patients with and without diabetes (Fig. 3).

The phenotype and presentation of kidney disease have been changing, especially in T2DM. New research both in experimental models and in patients will offer novel therapies in the future.

Prevention of kidney disease is extremely important, and we should endeavour all our resources to implement a preventive therapeutic approach.

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