Kidney Disease in Diabetic Patients

Subjects: Endocrinology & Metabolism

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Diabetic patients often present diabetic kidney disease (DKD), a burdensome complication that can be silent for years. The average time of onset of kidney impairment in diabetic patients is about 7–10 years. The clinical impact of DKD is dangerous not only for the risk of progression to end-stage renal disease and therefore to renal replacement therapies, but also because of the associated increase in cardiovascular events.

Keywords: diabetic kidney disease ; diabetes ; therapeutic inertia ; end-stage renal disease ; diabetic nephropathy ; antidiabetic drugs

1. Introduction

Diabetes mellitus (DM) is the leading cause of kidney failure globally [1]. Specifically, diabetic kidney disease (DKD), which is defined as elevated urine albumin excretion or reduced glomerular filtration rate (GFR) or both, is a serious complication that occurs in up to 40% of all diabetic patients [2].

The clinical and socio-economic impact of DKD is burdensome not only because of the risk of progression to end-stage renal disease (ESRD) and therefore to renal replacement therapies, but also because of the associated increase in cardiovascular (CV) risk [3][4]. A strict control of blood glucose is essential in DKD. Although many antidiabetic agents are currently available, the treatment of diabetes in DKD is challenging. Many antidiabetic drugs are contraindicated in advanced CKD, and others require dose adjustments due to an increased risk of drug toxicity as a result of reduced renal excretion [5][6].

2. DKD Risk Factors

Both genetic and environmental variabilities represent risk factors of disease progression. Besides the non-modifiable risk factors, such as family history, genetics, gender, age at diagnosis, and DM duration, lifestyle can be improved promoting healthy habits. It is important to maintain a proper glycemic control, blood pressure, avoid or quit smoking, reduce alcohol consumption, practice physical activity, follow a balanced diet and maintain a healthy lipidic profile [7].

It is of paramount importance to guarantee a structured education for patients and health care professionals to raise awareness to the role of DM and DKD prevention. Self-management knowledge should be used as an adjunct therapeutic option, especially in high-risk patients.

3. Pathophysiology of DKD

The pathophysiology of DKD is multifactorial and characterized by a critical metabolic impairment; the upstream influence of hyperglycemia leads to a dysregulated intracellular metabolism, inflammatory lesions, increased apoptosis processes and tissue fibrosis [8]. At the basis of DKD injury there are three crucial steps: (1) glomerular hypertrophy leading to hyperfiltration. Glomerular hyperfiltration is present in up to 75% of T1DM patients and up to 40% of patients with T2DM and is a typical feature of early DKD manifestations [9]; (2) glomerular and tubulointerstitial inflammation, related to chemokines, cytokines, and profibrotic factors activation; (3) dysregulated cellular apoptosis and changes in the extracellular matrix. These mechanisms lead to glomerular basement membrane thickening, podocyte depletion, mesangial matrix expansion, and tubular damage. All these factors may contribute to the progression of DKD, resulting in vascular remodeling, endothelial dysfunction, glomerulosclerosis, and tubulointerstitial fibrosis [10][11][12].

Different intracellular pathways demonstrated a driving role in the DKD process, stimulated by hyperglycemia. High blood glucose stimulates protein kinase C beta type (PKC-beta) and protein kinase C delta type (PKC-delta) activation in the renal cortex. This mechanism triggers the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the release of both interleukin (IL)-6 and the tumor necrosis factor (TNF)-α by endothelial and mesangial cells [13][14]. The

advanced glycation end-products species (AGEs) pathway not only alters the reactive oxygen homeostasis in a pro-oxidant way [15][16] but also contributes to the ultrastructural changes of the mesangial matrix, with a preferential localization to nodular lesions of DKD patients [17].

In addition to PKC and AGEs-guided mechanisms, more intracellular pathways seem to be implicated in the DKD insult. NF-κB, inducible nitric oxide synthase, JAK/STAT, and transforming growth factor-beta1/SMAD pathways are all leading to the production of proinflammatory molecules inducing extracellular matrix deposition and the differentiation/proliferation of myofibroblast in DKD patients [18][19][20][21].

4. Management of Diabetes Mellitus in the Transition from DKD to ESRD

A timely recognition of the risk factors for DKD progression can be crucial in decreasing morbidity and mortality in diabetic patients.

Several wake-up calls should alarm diabetic patients regarding their kidneys' health, and patients should be referred to a nephrologist earlier if they present rapid renal reduction, resistant hypertension, hyperkalemia, UACR exceeding 300 mg/g, or other urinary abnormalities [22].

A proper remodeling of lowering glucose therapy is one of the main points that should be evaluated in the evolution from DKD to ESRD. Diabetic patients with ESRD present high levels of blood urea nitrogen, leading to carbamylated hemoglobin production; these molecules are not distinguishable from glycosylated hemoglobin by electrophoresis, causing incorrect elevated levels of hemoglobin A1C [23]. Moreover, the reduced lifespan of red blood cells, iron deficiency, and erythropoietin-stimulating agents can lead to an undervaluation of glucose control [24].

Most oral diabetes drugs are contraindicated in ESRD and the pharmacological therapy should be balanced to avoid over- and undertreatment.

For DKD patients, the transitional ambulatory can represent an opportunity to be evaluated also for non-pharmacological treatments. Renal pre-emptive transplantation or combined pancreas-renal transplantation can represent a suitable option for selected subjects, especially for T1DM patients. Despite the significant improvement in DKD treatment in the last decades, these patients remain at higher risk of ESRD development and mortality; a pre-emptive transplant can strongly improve their quality of life and life expectancy [25].

5. Pharmacological Management of DKD—New Insights and Old Confirmations

5.1. RAS Blockade

DKD is a crucial harm in patients affected by DM because it represents a risk of CKD progression up to ESRD and increased CV morbidity and mortality. DKD treatment addresses both problems with first-choice drugs represented by renin-angiotensin system (RAS) blockade, including either angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB). These drugs played a pivotal role in reducing albuminuria and slowing GFR losses in several clinical trials, such as the Collaborative study (captopril) [26], RENAAL (losartan) [27], and the IRMA and IDNT studies (irbesartan) [28][29].

Particular attention should be paid to transient changes in the serum levels of potassium and creatinine after RAS blockade introduction. A dual blockade with ACEi/ARB or their association with either mineralocorticoid receptor antagonists (MRA) or a renin inhibitor is also discouraged.

5.2. Antidiabetic Drugs

Due to the reduced renal excretion, many antidiabetic drugs (substantially excreted via the kidney) are contraindicated or require dose adjustments in DKD patients to prevent hypoglycemia [30][31][32] (**Table 1**). Metformin has been shown to be safe and effective in glycemic control in patients with T2DM, but it is contraindicated if GFR <30 mL/min/1.73 m^2; SGLT2i, on the other hand, have low hypoglycemic effect in patients with impaired renal function, and therefore their use should be restricted in such patients [30][31].

Table 1. Dose adjustment for antihyperglycemic drugs in DKD.

Drug Class	Medications	Recommendation
Biguanides	Metformin	Contraindicated if GFR <30 mL/min/1.73 m^2 Not started in GFR 30–45 mL/min/1.73 m^2
SGLT2 inhibitors	Empagliflozin	Avoid use or discontinue if GFR <45 mL/min/1.73 m^2
	Canagliflozin	Avoid use if GFR <30 mL/min/1.73 m^2 Dose adjustment in GFR 30–59 mL/min/1.73 m^2
	Dapagliflozin	Contraindicated if GFR <30 mL/min/1.73 m^2 Not started in GFR 30–45 mL/min/1.73 m^2
First-generation sulfonylureas	Acetohexamide, tolazamide, tolbutamide, chlorpropamide	Avoid use
Second-generation sulfonylureas	Glyburide	Avoid use
	Glimepiride	Start cautiously in GFR <15 mL/min/1.73 m^2
	Glipizide	No dose adjustment
	Glicazide	No dose adjustment
Alpha-glucosidase inhibitors	Acarbose	Contraindicated if GFR <30 mL/min/1.73 m^2
GPL-1 receptor agonists	Exenatide	Contraindicated if GFR <30 mL/min/1.73 m^2
	Lixisenatide	Contraindicated if GFR <15 mL/min/1.73 m^2
	Liraglutide	No dose adjustment
	Albiglutide	No dose adjustment
	Dulaglutide	No dose adjustment
Thiazolidinediones	Pioglitazone	No dose adjustment
	Rosiglitazone	No dose adjustment
Meglitinides	Repaglinide	Start cautiously in GFR <15 mL/min/1.73 m^2
DPP-4 inhibitors	Sitagliptin	Lower dosage
	Vildagliptin	Lower dosage
	Saxagliptin	Lower dosage
	Alogliptin	Lower dosage
	Linagliptin	No dose adjustment
Insulins	Dose adjustment based on patient response	

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GFR = glomerular filtration rate; GPL-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose cotransporter 2.

5.3. Dyslipidemia Management

Elevated levels of triglycerides and low-density lipoprotein—cholesterol (LDL-c) are associated with an increased CV risk and the progression of CKD in patients with DKD. Thus, an evaluation of the lipid profile is indicated, and an appropriate pharmacological approach in patients with DKD is needed. Lipid-lowering therapy with statins was proven to have a protective effect on renal function by improving albuminuria and the estimated GFR [33]. However, since high doses of statins may be toxic in patients with GFR <60 mL/min/1.73 m^2, a dose adjustment is required [33] based on each patient's GFR [33] (**Table 2**). On the other hand, KDIGO guidelines suggest that statin treatment should not be started in DKD patients on dialysis [34].

Table 2. Dose adjustment for statins in DKD.

Statins	Normal to Mildly Decreased (GFR: ≥90 to 60–89 mL/min/1.73 m^2)	Mildly/Moderate Decreased to Kidney Failure (GFR: 45–59 to <15 mL/min/1.73 m^2)
Lovastatin	**No dose adjustment**	**NA**
Fluvastatin	**No dose adjustment**	**80 mg/day**
Atorvastatin	**No dose adjustment**	**20 mg/day**
Rosuvastatin	**No dose adjustment**	**10 mg/day**
Simvastatin/Ezetmibe	**No dose adjustment**	**20 mg/day**
Pravastatin	**No dose adjustment**	**40 mg/day**
Simvastatin	**No dose adjustment**	**40 mg/day**
Pitavastatin	**No dose adjustment**	**2 mg/day**

Abbreviations: GFR = glomerular filtration rate; NA = not available.

5.4. Antiplatelet Therapy

Antiplatelet agents are widely used in the secondary prevention of CV disease. DKD patients are at higher risk of thrombo-embolic events. However, these patients are also at high risk of bleeding. Therefore, evidence suggests that the use of antiplatelet agents in a multi-drug approach is effective in reducing CV risk. However, antiplatelet therapy as a primary prevention is to be avoided in patients with DKD [35].

6. Critical Issues on DKD Management: Evidence from Real-World Settings

Glycemic control in DKD patients is strongly recommended not only for cardiovascular prevention, but also to prevent DKD progression [36]. Glycemic management in patients affected by DKD is challenging due to several factors, such as therapeutic inertia, monitoring difficulties, and the complexity regarding the use of the available treatments [37]. Indeed, one of the main issues in glycemic control in DKD patients is that the risk of hypoglycemia increases with a decreasing GFR, mainly because of the altered pharmacodynamic and pharmacokinetic profiles of antidiabetic drugs and the reduced kidney mass [38].

Along with glycemic control, the control of blood pressure and blood cholesterol levels is crucial to slow DKD progression and prevent its macrovascular and microvascular complications [39][40].

Due to their complex clinical conditions, DKD patients generally take many drugs to slow the progression of their renal disease, prevent specific complications, and manage comorbidities [41], thus leading to an increased risk of experiencing adverse drug reactions (ADRs) and drug-drug interactions. Moreover, the worsening of renal function is often caused by the use of nephrotoxic drugs, especially when used for a long period and at high dosages [42]. All these factors make appropriate drug prescribing more challenging in such a population of patients.

7. Factors Related to Therapeutic Inertia

Several factors may influence the need for the intensification of treatment, including ineffective diet and exercise initiatives, limited pharmacologic armamentarium, conservative management, adverse events, poor compliance, underlying physiopathology, limited resources, and suboptimal healthcare systems [43].

Barriers to treatment intensification can be categorized into three levels (**Figure 1**):

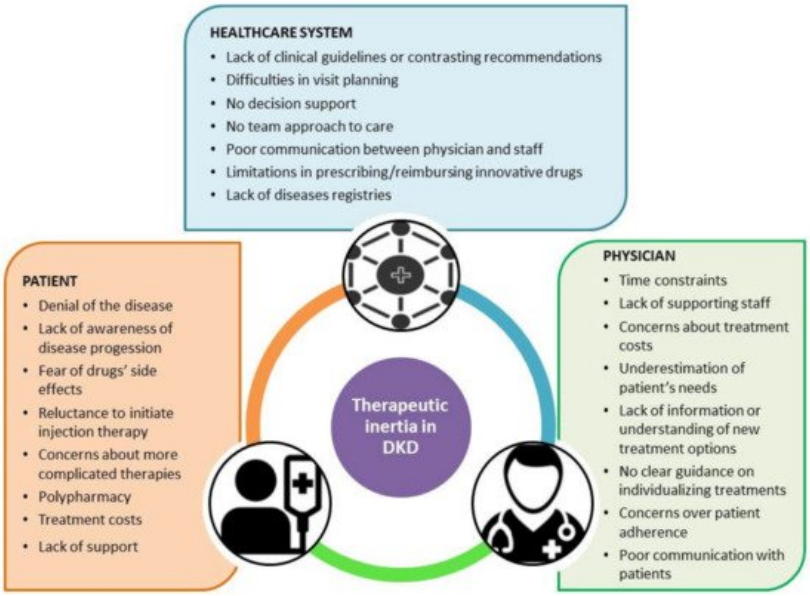

Figure 1. Factors related to therapeutic inertia.

8. Strategies to Optimize the Management of DKD Patients

(A) Patient level: Diabetic patients should be conscious of the care plans and target value for the best DKD management: glucose, creatinine, GFR, blood urea nitrogen, phosphorus, calcium, PTH, Vitamin D, albumin, lipid, potassium, and hemoglobin targets. A proper management of blood pressure control and pulse pressure targets is essential. The patient should be motivated to follow a balanced dietary intake and know the best nutrients to choose to reach the desirable glucose values.

(B) Clinician level: High-quality diabetes care requires creating a multi-specialist team that can gain a complete vision of the patient's status and study the best strategies for implementing cures. Bridging fundamental approaches to care optimization for general practitioners, diabetologists, dieticians, nephrologists, and pharmacologists is critical. The team must perform a "treat to success" management approach rather than a "treat to failure" strategy [44]. Specialists and general practitioners should co-work to make the patient conscious of the importance of a proper glycemic and pressure control. An adequate doctor-patient communication should be promoted. The team must constantly ensure that the patient fully understands the therapeutic modifications and his health status variations. Psychological help should be guaranteed by professionals, especially to treat depression-related symptoms or to gradually overcome the denial of the disease.

An adequate educational training should also be performed for the clinicians, who must test their own performance and be aware of medical updates. Clinical audits must also be an integral part of the educational programs for health care professionals. Finally, cost-benefit data on drug use must be clearly explained and presented to the patient, who must freely evaluate and understand all the therapeutic strategies.

(C) System level: Specialized efforts to identify patients at high risk of DKD progression are of pivotal importance to program primary care strategies and to direct clinical resources. The health system must promote the necessary acts to improve the quality of care and establish clear guidelines among the different scientific societies to recognize subjects who may benefit from a closer control, intensive glucose-lowering treatment, or particular therapies. An implementation of data on therapeutic inertia should be performed globally: most of the studies were conducted in North America and in Europe, while in other Countries data are still scarce [45]. For this reason, DKD registries must be improved worldwide to monitor the standards of care and to establish the best strategies.

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