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# REVIEW OF KIDNEY DISEASE AS A CHRONIC COMPLICATION OF TYPE 2 DIABETES MELLITUS

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**Abstract**: Introduction: Metabolic changes caused by diabetes mellitus can lead to the development of acute and chronic complications, such as nephropathy and neuropathy. Severe chronic kidney disease (CKD) is one of the main complications related to type 2 diabetes (T2DM) with a 10 times higher prevalence among diabetics. Given this, there is much speculation about the impact that diabetes has as a predisposing factor for CKD. Therefore, the present work sought to understand how kidney disease is a complicating factor for patients with diabetes and the possible treatments available. Methodology: the study is a review, where articles from different databases were analyzed, such as PubMed, Scielo and Elsevier, in addition to the Clinical Guidelines of the Brazilian Society of Diabetes, using the key words: diabetes, kidney disease, disease diabetes, risk factors and clinical studies (in Portuguese and English) using the Boolean descriptors "and" and "or". Articles referring to the years 2015 to 2021 that had at least two key words in the title were collected. Results: Diabetes is one of the main factors for the progression of kidney damage, largely due to functional and structural changes in kidney cells in response to excessive influx of cellular glucose. Diabetes mellitus and associated CKD lead to a higher risk of cardiovascular morbidity and all-cause mortality, in addition, patients with diabetes compared to non-diabetics have a higher rate of developing end-stage renal disease. For patients with chronic kidney disease, glycated hemoglobin (HbA1c) close to 7% is recommended as a treatment goal for DM2 for those with nephropathy without severe dysfunction and HbA1C < 7.5-8% for those with advanced kidney disease or on dialysis therapy Conclusion: This review described kidney disease as a complicating factor for patients with diabetes.

**Keywords:** Diabetes; complications; kidney disease.

## INTRODUCION

According to the World Health Organization (2019), diabetes comprises metabolic disorders characterized by hyperglycemia, with defects in insulin secretion and/or insulin action and consequently disorders in the metabolism of carbohydrates, fats and proteins.

In the current classification, there are two main types: type 1 diabetes mellitus (DM1) and type 2 diabetes mellitus (DM2); the distinction has been based on the age of onset, the degree of loss of β-cell function, the degree of insulin resistance, the presence of autoantibodies (WORLD HEALTH ORGANIZATION, 2019).

The choice of glucose-lowering medications is made according to the risk of hypoglycemia and the individual's individuality; therefore, when planning diabetes treatment, acute and chronic complications are considered (AMERICAN DIABETES ASSOCIATION, 2019). Chronic complications are related to vascular diseases (macrovascular and microvascular), which include coronary, cerebral and peripheral vascular events, nephropathy, retinopathy and neuropathy (CASSYANO; REIS, 2016).

Chronic kidney disease (CKD) is one of the main microvascular complications of DM2. The proportion of end-stage kidney disease due to diabetes only varies between 10% and 67%, with a prevalence of 10 times greater in people with diabetes than those without (INTERNATIONAL DIABETES FEDERATION, 2019).

The safest antidiabetic drug in severe CKD is insulin, but there are also several oral drugs that can be used with different recommendations, with dose adjustment and monitoring of adverse effects, and oral hypoglycemic drugs have several mechanisms for reducing glucose and have effects distinct adverse effects (ABI-ABIB, 2015; AKHTER; UPPAL, 2020).

Therefore, the present work seeks to understand how kidney disease is a complicating factor for patients with diabetes and the possible treatments available.

## METHODOLOGY

To prepare this review, scientific articles were searched in the PubMed databases of the *National Center for Biotechnology Information Search Database, Scientific Electronic Library Online (*SCIELO*), Science Direct* (Elsevier) with the key words: diabetes, kidney disease, kidney disease of diabetes, risk factors, and clinical studies (in Portuguese and English), the Boolean descriptors "and" and "or" were used. Articles referring to the years 2015 to 2021 that had at least two key words in the title were collected. In addition, there was access to Brazilian and American clinical guidelines, such as the Clinical Guidelines of the Brazilian Diabetes Society and the American Diabetes Association.

## RESULTS

Diabetes mellitus has affected humans since ancient times. Aretaeus of Cappadocia (81-138 B.C.) first described it as the "melting of flesh...into urine," accompanied by an insatiable and terrible sensation of thirst. In the Middle Ages the disease was known as "the evil of urination", so the term diabetes refers to the flow of fluid through a siphon, and mellitus comes from the word honey (SILVERTHORN, 2017).

"Diabetes is characterized by abnormally high plasma glucose concentration (hyperglycemia) resulting from inadequate insulin secretion, abnormal target cell response, or both" (SILVERTHORN, 2017). In type 2 diabetes, hyperglycemia results from insulin resistance and over time, there is inadequate production of this hormone by pancreatic beta cells (INTERNATIONAL DIABETES FEDERATION, 2019).

Insulin resistance is a condition in which tissue cells, mainly skeletal muscle and adipocytes, do not respond to this hormone and consequently there is no entry of glucose into these cells; Oxidative stress, inflammation, insulin receptor mutation, endoplasmic reticulum stress and mitochondrial dysfunction are believed to contribute to this condition (YARIBEYGI et al., 2018).

In the review by Kyrou and collaborators (2020), it was described that insulin resistance is correlated with the accumulation of visceral and ectopic fat (for example, in the liver, skeletal muscles and heart), therefore central/visceral obesity is recognized as a factor in risk for DM2.

Type 2 diabetes is the most common type of diabetes, accounting for around 90-95% of all diabetes. (AMERICAN DIABETES ASSOCIATION, 2019). In 2019, 488 million adults, aged between 20-99 years, were confirmed to have the disease worldwide (SINCLAIR et al., 2020). That year, there were 351.7 million diabetics aged 20–64 years, with countries such as China, India and the United States of America having the highest numbers and in Brazil the number was 16.8 million people (INTERNATIONAL DIABETES FEDERATION, 2019). In the age group between 65-99 years old, an estimated 135.6 million people have diabetes, with Brazil accounting for 6.1 million, ranked 5th in the ranking of countries (SINCLAIR et al., 2020).

There are several causes for DM2. Genetic and lifestyle factors are important in the onset of the disease; lifestyle factors include: diet, physical activity, smoking, alcohol consumption (HAN et al., 2020). Furthermore, metabolic syndrome, which represents a set of independent cardio-metabolic risks (including obesity, hypertension, dyslipidemia and glucose intolerance), correlates with a higher risk of type 2 diabetes, with hypertension and dyslipidemia being risk factors. independently

(KYROU et al., 2020).

In most cases, the disease is asymptomatic and less frequently they present classic symptoms of hyperglycemia (polyuria, polydipsia, polyphagia and unexplained weight loss), with the diagnosis being made through routine laboratory tests or when there are manifestations of chronic complications (BRAZILIAN DIABETES SOCIETY, 2019).

The diagnosis of the disease adopted by the Brazilian Diabetes Society - SBD (2019) is based on the parameters adopted by the American Diabetes Association, which uses laboratory tests of fasting blood glucose, blood glucose 2 hours after an oral glucose tolerance test (OGTT) and glycated hemoglobin; the values are described in Table 1:

| Exam | Normal | Prediabetes | Diabetes |
|---|---|---|---|
| Glycemia 2 hours after OGTT with 75 g of glucose (mg/dL) | < 100 | 100 to 125 | ≥ 126 |
| Glycemia 2 hours after OGTT with 75 g of glucose (mg/dL) | < 140 | 140 to 199 | ≥ 200 |
| glycated hemoglobin (%) | < 5,7 | 5,7 to 6,4 | ≥ 6,5 |

Table 1 - Diagnostic criteria for diabetes mellitus recommended by the Brazilian Diabetes Society.

TOTG: oral glucose tolerance test.

Source: Adapted from the Brazilian Diabetes Society, 2019

In the systematic review and meta-analysis conducted by Uusitupa and collaborators (2019), they found evidence that the prevention of type 2 diabetes can be achieved through lifestyle changes, with weight reduction through dietary changes such as fiber intake, increase the use of whole grain products, fruits and vegetables, and increase physical activity.

The forms of treatment are through lifestyle modifications that include a healthy diet, regular physical activity, education about the disease, guidelines for adequate control of glycemia, lipids, blood pressure and weight, in addition, there are therapies pharmacological treatments with oral or injectable antidiabetics, in monotherapy or combination, depending on the profile of each individual (CONITEC, 2020).

Chronic kidney disease is a public health problem, characterized by progressive loss of nephron function with consequent loss of the ability to filter the blood and maintain homeostasis (AGUIAR et al., 2020).

Kidney function can be determined through the Glomerular Filtration Rate (GFR). According to the Clinical Guidelines for the Care of Patients with Chronic Kidney Disease (CKD) of the Ministry of Health, the parameters used to diagnose CKD are: presenting in 3 consecutive months GFR < 60 mL/min/1.73 m2 or GFR ≥ 60 mL/ min/1.73 m2 associated with at least one marker of parenchymal renal damage (albuminuria, hematuria, hydroelectrolyte disorders, histological changes in renal biopsy) or changes in the imaging exam (BRASIL, 2014).

Once the diagnosis of CKD has been made, disease staging is defined based on GFR, classified as stage 1 (GFR ≥90 mL/min/1.73 m2), 2 (GFR 60-89 mL/min/ 1.73 m2), 3a (GFR 45–59 mL/min/1.73 m2), 3b (GFR 30–44 mL/min/1.73 m2), 4 (GFR 15–29 mL/ min/1, 73 m2) and 5 (GFR <15 mL / min / 1.73 m2), thus allowing a better structuring of treatment and patient prognosis, and in stages 1 to 3 the treatment is conservative (control of risk factors in progression), 4 and 5 non-dialysis is pre-dialysis (maintenance of conservative treatment and preparation for renal replacement therapy), and 5 dialysis uses renal replacement therapy (RRT) which consists of hemodialysis, peritoneal dialysis and kidney transplantation (BRASIL, 2014; CHEN et al., 2019).

GFR is determined through estimation

equations, such as the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) and MDRD (Modification of Diet in Renal Disease Study), which replaced the need for direct measurement in clinical practice, being estimated based on filtration markers that the most common is creatinine, a byproduct of creatine metabolism, for which laboratory tests have been standardized since 2003 (CHEN et al., 2019).

CKD is very prevalent in the general adult population. Data from the United States estimate a prevalence of 13.1% among adults, which has increased over time. In Brazil, estimates of the prevalence of the disease are uncertain (AMMIRATI, 2020). A study conducted by Malta and collaborators (2019) determined the prevalence of CKD in elderly Brazilian adults by estimating GFR, and out of 7,457 participants, a prevalence of 6.4% was found for GFR ≥ 30 to < 60 mL/ min/1.73 m2, 0.1% for GFR ≥ 15 to < 30 mL/min/1.73 m2 and 0.2% for GFR < 15 mL/min/1.73 m2, being more common in elderly and women.

The delay of disease progression is related to the care of patients with CKD; the treatment of complications related to the pathology, such as anemia, mineral and bone disorders, hydroelectrolyte disorders, metabolic acidosis and cardiovascular disease; To prepare the patient for RRT and establish an immunization routine, multidisciplinary monitoring is necessary at all levels of treatment in these patients (AMMIRATI, 2020).

The main factors for the progression of kidney damage and the consequent loss of filtration are: diabetes, hypertension, hypercholesterolemia, smoking, alcohol consumption, obesity, diet and old age (AGUIAR et al., 2020).

Diabetes mellitus and associated CKD lead to a higher risk of cardiovascular morbidity and all-cause mortality, in addition, patients with diabetes compared to non-diabetics have a higher rate of developing end-stage renal disease. In a systematic review and meta-analysis carried out, the authors concluded that DM was a strong risk factor for CKD and end-stage renal disease in men and women (CARRETERO-GOMEZ; LORIDO, 2018).

Diabetes kidney disease (DRD), also known as diabetic nephropathy, is a complication that affects patients with DM without long-term glycemic control (LIN et al., 2018). Amorim and collaborators (2019) report the pathogenesis of DRD through functional and structural changes in kidney cells as a response to metabolic stress induced by excessive influx of cellular glucose, through the activation of specific metabolic pathways linked to redox imbalance and inflammation.

Clinically, DRD is related to renal abnormalities that persist for a period equal to or greater than 3 months, with urinary albumin excretion (US) >30 mg/24h or albumin-creatinine ratio (ACR) ≥30 mg/g creatinine or glomerular filtration rate (TGF) < 60 mL/min/1.73 m2, after a period of hyperfiltration or structural abnormalities present in individuals with a previous diagnosis of DM (AMORIM et al., 2019).

> DRD interventions mainly consist of correction of hyperglycemia, hypertension and dyslipidemia and lifestyle modification. Primary prevention represents the prevention of normoalbuminuria to microalbuminuria, while secondary prevention represents the prevention of microalbuminuria to macroalbuminuria. Multiple interventional managements with control of blood glucose, blood pressure and lipids and smoking cessation can significantly improve the prognosis of cardiovascular events and help slow the progression of kidney disease, including macroalbuminuria and decreased eGFR for patients with type 2 DM and DRD (IN et al., 2018).

In patients with chronic kidney disease, the treatment goal for DM2 is recommended to be glycated hemoglobin (HbA1c) close to

7% for nephropathy patients without severe dysfunction and HbA1C < 7.5-8% for those with advanced kidney disease (glomerular filtration rate -GFR < 10 ml/min/1.73m2) or undergoing dialysis therapy (ABI-ABIB, 2015).

For Lin and colleagues (2018), glycemic control in patients with diabetes must be individualized according to hypoglycemia, underlying CKD or cardiovascular disease status and age, in individuals with multiple comorbidities, limited life expectancy and risks of hypoglycemic episodes, target HbA1c levels can be extended above 7.0%.

Renal tubular sodium/glucose cotransport inhibitors (SGLT2 inhibitors) and glucagon-like peptide-1 (GLP-1) analogues are oral antidiabetics that can reduce the risks of CKD progression, events cardiovascular disease and hypoglycemia, therefore they are used in patients with kidney disease (AMERICAN DIABETES ASSOCIATION, 2019).

SGLT2 inhibitors act to inhibit glucose reabsorption and must not be used in patients with GFR < 30 mL/min/1.73m2, while long-acting GLP-1 analogues can be used at any stage of DRD (BRAZILIAN SOCIETY OF DIABETES, 2019).

## CONCLUSION

Studies reported that patients with diabetes had a higher rate of developing end-stage renal disease, clinically manifested through changes in GFR and protein excretion.

Interventions involve lifestyle changes in order to reduce the progression of the disease, with glycemic control being individualized for each patient, as associated comorbidities are considered.

Given this, this review described kidney disease as a complicating factor for patients with diabetes.

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