Diabetic Nephropathy: Pathophysiology, Diagnosis and Treatment

Nefropatia Diabética: Fisiopatologia, Diagnóstico e Tratamento
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RESUMO
A nefropatia diabética é uma complicação grave do diabetes mellitus, que pode evoluir para doença renal terminal. A patologia envolve hipertensão glomerular, hipertrofia renal e depósitos de proteínas na matriz extracelular, resultando em inflamação, fibrose e glomeruloesclerose. Por meio deste artigo objetiva-se descrever a fisiopatologia, diagnóstico e tratamento da nefropatia diabética, com base em uma revisão da literatura atual. Para tanto, procedeu-se à análise de artigos e estudos clínicos publicados até julho de 2024, utilizando bases de dados como PubMed, Google Acadêmico e Biblioteca Cochrane, focando em termos-chave relacionados à nefropatia diabética. Observou-se que a albuminúria, a estimativa da taxa de filtração glomerular e a presença de retinopatia diabética são importantes marcadores da nefropatia diabética [1]. Biomarcadores emergentes como NGAL e KIM-1 são promissores para detecção precoce de lesão renal [11]. O tratamento, sem terapias específicas, concentra-se no controle glicêmico e pressórico, manejo da albuminúria e mudanças no estilo de vida, com uso de medicamentos como IECA e iSGLT2 para proteção renal e redução de complicações cardiovasculares. Conclui-se que, apesar das intervenções, a progressão para doença renal terminal é comum, destacando a necessidade de novas terapias e uma melhor compreensão dos mecanismos subjacentes, além da identificação de biomarcadores confiáveis para monitorar a progressão da doença.
DESCRITORES: nefropatia, diabetes, albuminúria.

ABSTRACT
Diabetic nephropathy is a serious complication of diabetes mellitus, which can progress to end-stage renal disease. The pathology involves glomerular hypertension, renal hypertrophy and protein deposits in the extracellular matrix, resulting in inflammation, fibrosis and glomerulosclerosis. This article aims to describe the pathophysiology, diagnosis and treatment of diabetic nephropathy, based on a review of current literature. To this end, we analyzed articles and clinical studies published until July 2024, using databases such as PubMed, Google Scholar and the Cochrane Library, focusing on key terms related to diabetic nephropathy. It was observed that albuminuria, estimated glomerular filtration rate and the presence of diabetic retinopathy are important markers of diabetic nephropathy [1]. Emerging biomarkers such as NGAL and KIM-1 hold promise for early detection of kidney injury [11]. Treatment, without specific therapies, focuses on glycemic and blood pressure control, albuminuria management and lifestyle changes, with the use of medications such as ACE inhibitors and iSGLT2 for renal protection and reduction of cardiovascular complications. It is concluded that, despite interventions, progression to end-stage renal disease is common, highlighting the need for new therapies and a better understanding of the underlying mechanisms, in addition to the identification of reliable biomarkers to monitor disease progression.
DESCRIPTORS: nephropathy, diabetic, albuminuria.

RESUMEN
La nefropatía diabética es una complicación grave de la diabetes mellitus que puede progresar a enfermedad renal terminal. La patología implica hipertensión glomerular, hipertrofia renal y depósitos de proteínas en la matriz extracelular, lo que resulta en inflamación, fibrosis y glomeruloesclerosis. El objetivo de este artículo es describir la fisiopatología, el diagnóstico y el tratamiento de la nefropatía diabética, basándose en una revisión de la literatura actual. Para ello, se realizó un análisis de artículos y estudios clínicos publicados hasta julio de 2024, utilizando bases de datos como PubMed, Google Académico y la

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Biblioteca Cochrane, enfocándose en términos clave relacionados con la nefropatía diabética. Se observó que la albuminuria, la estimación de la tasa de filtración glomerular y la presencia de retinopatía diabética son importantes marcadores de la nefropatía diabética [1]. Biomarcadores emergentes como NGAL y KIM-1 son prometedores para la detección temprana del daño renal [11]. El tratamiento, sin terapias específicas, se centra en el control glucémico y de la presión arterial, el manejo de la albuminuria y los cambios en el estilo de vida, con el uso de medicamentos como los IECA y los iSGLT2 para la protección renal y la reducción de las complicaciones cardiovasculares. Se concluye que, a pesar de las intervenciones, la progresión a enfermedad renal terminal es común, lo que resalta la necesidad de nuevas terapias y una mejor comprensión de los mecanismos subyacentes, además de la identificación de biomarcadores confiables para monitorear la progresión de la enfermedad.
DESCRIPTORES: nefropatía; diabetes; albuminuria.

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INTRODUCTION

Diabetes mellitus and prolonged hyperglycemia generate, among various types of complications, diabetic nephropathy. This is one of the most serious and common complications of DM. The progression of diabetic nephropathy begins with microalbuminuria and can progress to macroalbuminuria with the passage of larger amounts of protein through the glomerular capillary membranes, leading to end-stage renal disease when these patients are not treated properly.

Changes in glomerular hemodynamics, inflammation, and fibrosis are primary mediators of damage to renal tissue. The mechanisms involved in the pathophysiology include glomerular hypertension, renal hypertrophy, and changes in glomerular structure. The changes involve protein deposition in the extracellular matrix, thickening of the glomerular basement membrane, and ultimately interstitial fibrosis and glomerulosclerosis [7].

The main marker for the diagnosis of diabetic nephropathy is the presence of albuminuria. Assessment of renal function, the presence of diabetic retinopathy, and exclusion of other renal diseases are also important criteria [13].

Due to the absence of specific therapies for diabetic nephropathy, treatment is based on slowing the progression of renal damage and its complications. To this end, treatment focuses on intensive glycemic control, blood pressure control, management of albuminuria, and lifestyle changes for the patient. New, more specific treatments are under investigation with potential for future use in the prevention, treatment, and delay of kidney disease triggered by diabetic nephropathy (Unmanath and Lewis, 2018).

OBJECTIVE

The objective of this article is to review the main aspects of diabetic nephropathy, addressing: the pathophysiological mechanisms involved in its development, the diagnostic methods available and under investigation, and current and emerging therapeutic strategies.

METHODOLOGY

This article aimed to identify the main definitions and advances in diabetic nephropathy, its pathophysiology, diagnosis, and treatment.

To this end, the authors reviewed evidence-based literature sources that served as the basis for the main guidelines on diabetic nephropathy.

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The review was based on articles and clinical studies published up to July 2024. Searches were conducted in the primary databases PubMed, Google Scholar, and Cochrane Library. The searches involved the keywords "diabetic nephropathy," "pathophysiology diabetic nephropathy," "diagnosis diabetic nephropathy," and "treatment diabetic nephropathy."

Relevant information was selected and summarized by the authors of the article. The authors synthesized the results of the literature to present a comprehensive overview of the current understanding of the pathophysiology and diagnosis of diabetic nephropathy, highlighting challenges and emerging therapeutic approaches.

DISCUSSION

Diabetes mellitus (DM) is the leading cause of chronic kidney disease (CKD) in patients starting renal replacement therapy, including in Brazil[6].

There are several forms of diabetes-related kidney disease. In view of this, in 2007, the Kidney Disease Outcomes Quality Initiative (KDOQI) proposed the use of the term Diabetic Kidney Disease (DKD), which corresponds to a clinical diagnosis based on the detection of albuminuria, decreased glomerular filtration rate (GFR), or both, in the diabetic population. (SANKAR et al, 2021; BRAZILIAN DIABETES SOCIETY, 2019-2020). The term Diabetic Nephropathy (DN) encompasses patients with persistent proteinuria and is usually associated with high blood pressure (BP). Statistically, DRD with albuminuria can affect 30 to 50% of patients with DM2, and in about 1/5 of cases, an isolated reduction in GFR is observed [6].

Hyperglycemia plays a central role in the development of the disease through different mechanisms. Glomerular hemodynamic changes, oxidative stress, inflammation, interstitial fibrosis, and tubular atrophy occur, leading to kidney damage [17].

In the context of inflammation caused by persistently high blood glucose levels, there is an increase in the production of angiotensin II, the end product of the activation of the renin-angiotensin-aldosterone system (RAAS) [4]. This hormone plays an important role in the pathophysiology of DRD, and reducing its levels is one of the pillars of treatment to slow the progression of the disease.

Angiotensin II, in addition to its known systemic vasoconstrictor effect, promotes vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole in the kidneys, as well as stimulating mesangial cell and tubular epithelial cell hypertrophy and the production of cytokines such as TGF-beta, which contributes to glomerular sclerosis, leading to progressive degeneration of renal function [4].

The early stages of the disease are marked by glomerular hyperfiltration and increased glomerular filtration rate. With the persistence of deleterious factors, it progresses to microalbuminuria, macroalbuminuria, and reduced GFR [12].

According to Salgado et al., the natural history of the disease is classically divided into four stages:

Stage 1: Hyperfiltration - increased GFR and normoalbuminuria. The reduction in afferent arteriolar resistance and increased efferent arteriolar resistance lead to increased glomerular pressure, favoring protein filtration.

Stage 2: Microalbuminuria or incipient nephropathy. Persistently high intraglomerular pressure favors protein filtration. At this stage, urinary albumin excretion ranges from 30 to 300 mg/24 h.

Stage 3: Proteinuria or clinical nephropathy. Urinary albumin excretion exceeds 300 mg/24 h and there is a progressive decline in GFR.

Stage 4: End-stage renal disease - Chronic kidney disease established, in dialysis and kidney transplant programs.

In about 30% of patients, albuminuria may regress. Reduced urinary albumin excretion (UAE) is associated with a slowdown in the decline of GFR, as well as a reduction in cardiovascular risk [6].

DN screening is a means of early identification and intervention in the disease. It is essential to start screening in patients with type 2 DM shortly after diagnosis. In the case of patients with type 1 DM, screening is indicated after 5 years, with the exception of diagnoses made at puberty and persistently decompensated cases, which should be screened regardless of these indications[6].

Renal assessment is performed using markers of renal injury through laboratory tests with GFR estimation and USG measurement. The latter is a low-cost technique performed on a 24-hour urine sample, which identifies the presence of albumin in the urine [15].

GFR can be estimated using various formulas, the most commonly used being MDRD and CKD-EPI. It is considered a better way to estimate glomerular filtration than the use of serum creatinine alone, but it is less accurate in older patients [1].

The test of choice for screening for albuminuria is the albumin/creatinine ratio in a urine sample—preferably the first urine of the morning, given its greater reliability—although the gold standard is the protein/albumin ratio in a 24-hour urine collection – with the first morning urine of the collection discarded and all others included up to and including the first urine of the following day. Given that albumin excretion varies with different conditions, the clinician can only assume that the patient has albuminuria when its presence is verified in at least 2 out of 3 samples taken over 3 months [1].

Incipient diabetic nephropathy is

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determined by an increase in USG in urine with values of 30-299 mg/min, known as microalbuminuria. Clinical diabetic nephropathy, on the other hand, is when there is an excessive presence of proteinuria or USG levels are above 300 mg/min, known as macroalbuminuria [15].

An ideal biomarker for acute kidney injury would be one that is easily measurable, without interference from other biological variables, and capable of both early detection of kidney damage and stratification of risk. Among the most studied emerging biomarkers are: NGAL, interleukin-18, KIM-1, cystatin-C, L-FABP, NAG, netrin-1, vanatin-1, and MCP-1. Of these biomarkers, NGAL is the most widely used in clinical studies, NGAL and L-FABP are the earliest, while KIM-1 and IL-18 are detected later with better specificity[11].

NGAL (neutrophil gelatinase-associated lipocalin) has been found to be a useful predictor in the early stages of ARF, working well with urine or plasma samples. Studies in animal models under renal ischemia have shown that NGAL can be detected early within two hours after renal ischemia. In addition, NGAL levels had prognostic value for clinical outcomes such as the need for dialysis and mortality. NGAL levels seem to predict ARF in children with greater accuracy than in adults. Unfortunately, high extrarenal production in response to systemic stress can increase its urinary excretion in the absence of ARF, as well as increase in CKD and not only in acute cases, which can confuse its interpretation [11].

KIM-1 (kidney injury molecule-1), on the other hand, is not detectable in normal kidney tissue or urine, but is expressed at very high levels in dedifferentiated cells of the proximal renal tubular epithelium in human and rodent kidneys after ischemic or toxic injury [11]. In addition, it is considered by US and European health regulatory agencies as a specific and highly sensitive urinary marker for monitoring drug-induced kidney disease. The expression and urinary level of KIM-1 also correlate with kidney damage in various kidney diseases, such as diabetic nephropathy, focal glomerulosclerosis, IgA nephropathy, graft rejection, among others. It is also believed that KIM-1 plays an important role in the repair and regeneration capacity of the renal tubules [5].

Primary prevention aims to prevent progression to end-stage renal disease, intervene in cardiovascular events, and prevent death. To this end, risk factors for progression, such as hyperglycemia, hypertension, albuminuria, dyslipidemia, smoking, obesity, poor diet, and physical inactivity, must be addressed[8].

Adequate blood pressure control slows the progression of nephropathy. Hypertensive diabetics without albuminuria should be treated with angiotensin-converting enzyme (ACE) inhibitors as the first choice. There is insufficient evidence that angiotensin receptor blockers are specifically beneficial for diabetic nephropathy. However, they can be used in patients who cannot tolerate ACE inhibitors [2].

Moraes, Colicigno, and Saccheti (2009) describe that several studies have shown that protein-restricted diets have a nephroprotective effect. A slowdown in the decline in glomerular filtration rate in patients with macroalbuminuric DM1 and a reduction in urinary albumin excretion in patients with microalbuminuric DM1 have already been demonstrated.

Quitting smoking slows the progression of CKD in diabetics, but this has not been demonstrated in non-diabetic patients. However, smoking is associated with more severe proteinuria [2].

Secondary prevention consists of a set of therapeutic measures instituted after the onset of renal dysfunction and albuminuria. Sulfonylureas, glipizide, and gliclazide undergo almost complete hepatic metabolism, generating inactive metabolites. Renal function does not affect clearance or half-life, and they should be used with caution and dose titration when GFR is < 30 mL/min/1.73 m^2. Treatment of DM2 patients on hemodialysis is safe with both glipizide and sitagliptin, provided that their doses are adjusted. DPP-4 inhibitors can be considered as monotherapy in patients who are intolerant or have contraindications to Metformin, such as patients with chronic kidney disease, particularly those at high risk of hypoglycemia [8].

Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) are drugs used as additional renal protection therapy. They work by reducing the risk of renal disease progression in patients with diabetic nephropathy who are already taking antihypertensive drugs. In addition, they reduce the incidence of cardiovascular disease. The drugs representing the class of SGLT2 inhibitors available on the market are: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin, and Sotagliflozin [8].

The Ministry of Health, through Ordinance No. 7, February 28, 2024, incorporated Dapagliflozin for the treatment of type 2 diabetes mellitus within the scope of the SUS. Its use is recommended in individuals aged ≥ 40 years with established cardiovascular disease (previous acute myocardial infarction, previous coronary artery bypass grafting, previous coronary angioplasty, stable or unstable angina, previous ischemic stroke, previous transient ischemic attack, and heart failure with ejection fraction below 40%), or; men ≥ 55 years of age or women ≥ 60 years of age at high risk of developing cardiovascular disease, defined as having at least one of the following cardiovascular risk factors: systemic arterial hypertension, dyslipidemia, or smoking.

The recommended dose of dapagli-

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flozin is 10 mg once daily, and is not indicated for patients with GFR below 25 mL/min/1.73 m2, noting that the efficacy of this drug is lower in patients with moderate to severe renal impairment (glomerular filtration rate less than 45 mL/min/1.73 m2) or renal failure.

CONCLUSION:

The development and progression of diabetic nephropathy are influenced by multiple risk factors, including chronic hyperglycemia, hypertension, and the presence of comorbidities. Therefore, its therapeutic approach must be multifactorial.

Management involves multiple strategies such as strict glycemic control, blood pressure control (usually using medications that involve the renin-angiotensin-aldosterone system), dyslipidemia control, and lifestyle changes such as diet, weight loss, physical exercise, and smoking cessation.

However, even with optimized treatment and good adherence to non-pharmacological measures, the progression of diabetic nephropathy cannot always be stopped, and many patients eventually develop end-stage renal disease.

This fact highlights the need for a better understanding of the underlying mechanisms of diabetic nephropathy. Furthermore, it shows the importance of developing new and effective therapies to delay the onset and progression of diabetic nephropathy. This includes the identification of reliable biomarkers to monitor disease progression, considering that most patients may not have albuminuria in the early stages of the disease.

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