DIABETIC NEPHROPATHY AS A RESULT OF UNCONTROLLED HYPERGLYCEMIA

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ABSTRACT

Objective: to investigate the relationship between uncontrolled hyperglycemia and the development of diabetic nephropathy.

Methods: Integrative review of the literature, carried out in June 2024, in the virtual databases Virtual Health Library, Medical Literature Analysis and Retrieval System Online and Google Scholar using the descriptors “Diabetic Nephropathies”, “Glomerular Filtration Rate”, “Hyperglycemia” and “Diabetes Mellitus”, as well as “Diabetic Nephropathies”, “Glomerular Filtration Rate”, “Hyperglycemia” and “Diabetes Mellitus” selected by DeCS and MeSH Descriptors, related to the Boolean operator AND in all databases.

Results and Discussion: after completing the methodological procedures, 12 articles available on the VHL Portal, in the PubMed, VHL and Google Scholar databases were selected, which show that diabetic nephropathy is a serious and common complication of diabetes mellitus, characterized due to the progressive impairment of renal function, being one of the main causes of chronic kidney disease and terminal renal failure worldwide. The

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Diabetic Nephropathy as a Result of Uncontrolled Hyperglycemia

development of diabetic nephropathy is linked to glycemic control, with chronic hyperglycemia being a crucial factor in the pathogenesis of this condition.

Final Considerations: strict control of blood glucose and blood pressure, combined with pharmacological interventions and lifestyle modifications, constitutes the basis of effective management of diabetic nephropathy.

Keywords: Diabetic Nephropathies, Glomerular Filtration Rate, Hyperglycemia, Diabetes Mellitus.

NEFROPATIA DIABÉTICA COMO RESULTADO DA HIPERGLICEMIA NÃO CONTROLADA

RESUMO

Objetivo: investigar a relação entre a hiperglycemia não controlada e o desenvolvimento da nefropatia diabética.

Métodos: Revisão integrativa da literatura, realizada em junho de 2024, nas bases de dados virtuais Biblioteca Virtual em Saúde, Medical Literature Analysis and Retrieval System Online e Google Scholar utilizando os descritores "Diabetic Nephropathies", "Glomerular Filtration Rate", "Hyperglycemia" e "Diabetes Mellitus", bem como "Diabetic Nephropathies", "Glomerular Filtration Rate", "Hyperglycemia" e "Diabetes Mellitus" selecionados pelo DeCS e MeSH Descriptors, relacionados ao operador booleano AND em todos os bancos de dados.

Resultados e Discussão: após a realização dos procedimentos metodológicos, foram selecionados 12 artigos disponíveis no Portal BVS, nas bases de dados PubMed, BVS e Google Scholar, que mostram que a nefropatia diabética é uma complicação grave e comum do diabetes mellitus, caracterizada devido ao comprometimento progressivo da função renal, sendo uma das principais causas de doença renal crónica e insuficiência renal terminal em todo o mundo. O desenvolvimento da nefropatia diabética está ligado ao controle glicêmico, sendo a hiperglycemia crônica um fator crucial na patogênese dessa condição.

Considerações Finais: o controle rigoroso da glicemia e da pressão arterial, combinado com intervenções farmacológicas e modificações no estilo de vida, constitui a base do tratamento eficaz da nefropatia diabética.


ETNODESARROLLO SOSTENIBLE: UN ESTUDIO CIENTIOMÉTRICO

RESUMEN

Objetivo: investigar la relación entre la hiperoglucemia no controlada y el desarrollo de nefropatía diabética.


Resultados y Discusión: luego de completar los procedimientos metodológicos, se seleccionaron 12 artículos disponibles en el Portal de la BVS, en las bases de datos PubMed, VHL y Google Scholar, que muestran que la nefropatía diabética es una complicación grave y común de la diabetes mellitus, caracterizada por la progresión deterioro de la función renal, siendo una de las principales causas de enfermedad renal crónica e insuficiencia renal terminal a nivel mundial. El desarrollo de la nefropatía diabética está estrechamente relacionado con el control de la glucemia, siendo la hiperglucemia crónica un factor crucial en la patogénesis de esta afección.

Consideraciones finales: el control estricto de la glucemia y la presión arterial, combinado con intervenciones farmacológicas y modificaciones del estilo de vida, constituye la base del manejo eficaz de la nefropatía diabética.

Palabras clave: Nefropatías Diabéticas, Tasa de Filtración Glomerular, Hiperglucemia, Diabetes Mellitus.
1 INTRODUCTION

Diabetic nephropathy is a common complication of type 1 and type 2 diabetes, and is considered the leading cause of chronic kidney disease worldwide. The condition arises when high blood sugar levels damage the small blood vessels in the kidneys, preventing them from functioning properly (Mohandes et al., 2023).

According to Jung and Yoo (2022), about 20 to 30% of diabetic patients are believed to develop diabetic nephropathy, and this may be even more common in patients with uncontrolled hyperglycemia. The condition can affect the quality of life and increase the risk of death of patients, thus increasing concern about the treatment of this complication.

Although health care and proper treatment of diabetes can help prevent diabetic nephropathy, many diabetic patients still cannot control their blood sugar levels to prevent such a condition. Thus, awareness about the importance of diabetes control is fundamental for the prevention of diabetic nephropathy and other chronic complications (DeFronzo; Reeves; Awad, 2021).

In addition, according to Yamazaki and his collaborators (2021) diabetic nephropathy presents a great clinical challenge, because the condition is often asymptomatic in its early stages, making early diagnosis and proper treatment difficult. Treatment of diabetic nephropathy usually involves optimizing diabetes control through diet, exercise, and medication.

Even so, many diabetic patients are not always able to keep their blood sugar levels below target values, which can further affect the evolution of diabetic nephropathy. Given this, it is essential to have a multidisciplinary approach through the patient's team in order to maintain the appropriate blood sugar level (Hung et al., 2021).

In line with Jiang, Fang, and Li (2023), guidance on diabetic nephropathy is key to minimizing its incidence and offering a better prognosis to patients. It is essential that diabetic patients understand the risks and need for adequate care of diabetes in order to prevent or treat diabetic nephropathy early. It is the duty of health professionals to impart the knowledge essential for a change in lifestyle in order to prevent chronic complications of diabetes.
In addition to awareness and proper control of diabetes, it is important to highlight that diabetic nephropathy can be prevented or controlled through a healthy and balanced diet, rich in nutrients and poor in processed foods and refined sugars. In addition, regular exercise can help control blood glucose and prevent diabetic nephropathy, as well as other complications of diabetes (Pugliese et al., 2019).

Finally, as stated by Garofalo and his collaborators (2019), it is important to emphasize that the early diagnosis and treatment of diabetic nephropathy are fundamental for the preservation of renal function and the prevention of serious complications, such as renal failure and premature death. Therefore, diabetic patients should often have urine and blood tests to evaluate kidney function, especially if they have symptoms such as increased thirst, loss of appetite, and swelling in the legs and feet. Early diagnosis allows more effective treatment and can even save the patient's life. In view of this, the study consists of investigating the relationship between uncontrolled hyperglycemia and the development of diabetic nephropathy.

2 METHODS

This study is an integrative literature review, with a broad methodological approach, which allows the inclusion of experimental and non-experimental studies for a full understanding of the phenomenon studied.

This, in particular, was developed in six stages: I. Definition of the theme and elaboration of the guiding question; II. the establishment of the eligibility criteria; Database search; IV. Definition of information that would be extracted from the materials found; V. Evaluation and interpretation of results; VI. Synthesis of knowledge (Souza; Silva; Carvalho 2010; Gerin et al., 2022).

The research question was formulated from the PICo strategy, with the objective of investigating the relationship between uncontrolled hyperglycemia and the development of diabetic nephropathy, evaluating the physiopathological mechanisms involved, the risk factors, and the prevention and management strategies to reduce the progression of renal disease in diabetic patients.

In this study the PICo strategy considered (P - Population; I - Interest; Co - Context), in which, P = Patients with Diabetes Mellitus, I = Uncontrolled Hyperglycemia, Co = Diabetic Nephropathy. With this, the guiding inquiry consists of: How does uncontrolled hyperglycemia
contribute to the development and progression of diabetic nephropathy, and what strategies can be implemented to prevent and treat this complication in patients with diabetes?

Carried out in June 2024 aiming to collect national and international scientific articles, the search was given in the following databases: Virtual Health Library (VHL), Medical Literature Analysis and Retrieval System Online (MEDLINE/PUBMED) and Google Academic. The descriptors "Diabetic Nephropathies", "Glomerular Filtration Rate", "Hyperglycemia" and "Diabetes Mellitus" were used in VHL and Google Academic. In MEDLINE/PUBMED, the descriptors "Diabetic Nephropathies", "Glomerular Filtration Rate", "Hyperglycemia" and "Diabetes Mellitus" were used and the boolean operator "and" between the descriptors in both databases.

Articles published in English, Portuguese and Spanish were included between 2019 and 2024, since it is a subject little discussed and presents significant studies inserted in this time frame. Primary and systematic data studies and/or meta-analyzes were also considered. The inclusion of these has been found to be of high level of evidence, as well as representing revisions of significant clinical studies in today's study. Articles that do not answer the study’s query, which present gray literature and secondary studies (except the above-mentioned reviews) were excluded.

The selection of articles can be verified through the flowchart, with the recommendations of PRISMA 2020 (Page et al., 2021).

Figure 1
3 RESULTS

After the completion of the methodological procedures, 12 articles available in the PubMed database, VHL and Google Academic were selected. The year of publication ranged from 2019 to 2024. After applying the search syntax described in Table 3, 1,732 articles were found. The table mentioned above gives the detailed information of the studies chosen for the analysis.

Table 1

*Strategy used to perform searches of the databases. Rio Branco, AC, Brazil, 2024.*

<table>
<thead>
<tr>
<th>Base</th>
<th>Search Expressions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUBMED</td>
<td>((Diabetic Nephropathies) AND (Glomerular Filtration Rate) AND (Hyperglycemia) AND (Diabetes Mellitus))</td>
</tr>
<tr>
<td>VHL</td>
<td>(Diabetic Nephropathies) AND (Glomerular Filtration Rate) AND (Hyperglycaemia) AND (Diabetes Mellitus))</td>
</tr>
<tr>
<td>ACADEMIC GOOGLE</td>
<td>Diabetic Nephropathies AND Glomerular Filtration Rate AND Hyperglycaemia AND Diabetes Mellitus</td>
</tr>
</tbody>
</table>

Source: Prepared by the author.
### Table 2

**Publications included in the second author/year study, title, objective and main results. Rio Branco, AC, Brazil, 2024.**

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Title</th>
<th>Purpose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulaiman, 2019.</td>
<td>Diabetic nephropathy: recent advances in pathophysiology and challenges in dietary management</td>
<td>Summarize current advances in staging and molecular pathogenesis of ND.</td>
<td>Patient education seems to be the key to avoiding excess foods high in carbohydrates and proteins, favoring the inclusion of essential fats in your diet.</td>
</tr>
<tr>
<td>Maciel; Vasconcelos; Andrade, 2019.</td>
<td>Diabetic nephropathy - incidence and associated risk factors</td>
<td>Investigate the effects of combined use of leflunomide and benazepril on diabetic nephropathy (DN) in vivo and in vitro.</td>
<td>The combined use of leflunomide and benazepril could improve renal function and reduce kidney damage in ND rats and could reduce NF-γ, TGF-β and TRPC6 levels in ND rats and high glucose-induced RMCs.</td>
</tr>
<tr>
<td>Li et al., 2019.</td>
<td>Combination of leflunomide and benazepril reduces renal injury of diabetic nephropathy rats and inhibits high-glucose induced cell apoptosis through regulation of NF-κB, TGF-β and TRPC6</td>
<td>Investigate the effects of combined use of leflunomide and benazepril on diabetic nephropathy (DN) in vivo and in vitro.</td>
<td>The combined use of leflunomide and benazepril could improve renal function and reduce kidney damage in ND rats and could reduce NF-γ, TGF-β and TRPC6 levels in ND rats and high glucose-induced RMCs.</td>
</tr>
<tr>
<td>Bommel et al., 2020.</td>
<td>The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial</td>
<td>Compare the renal haemodynamic effects of dapagliflozin with gliclazide in type 2 diabetes.</td>
<td>The fact that renal vascular resistance was not increased by dapagliflozin suggests that this was due to postglomerular vasodilation rather than preglomerular vasoconstriction.</td>
</tr>
<tr>
<td>Wang et al., 2020.</td>
<td>Poor Control of Plasma Triglycerides Is Associated with Early Decline of Estimated Glomerular Filtration Rates in New-Onset Type 2 Diabetes in China: Results from a 3-Year Follow-Up Study</td>
<td>Explore the long-term impact of lipid control on the renal evolution of recently-onset type 2 diabetes mellitus (DM2).</td>
<td>This study emphasized the importance of long-term TG control in East Asian patients with newly-onset TG by DM2 may delay the decline of renal function in the early stage of DRD, and reversal of hypertriglyceridaemia may undo past risks.</td>
</tr>
<tr>
<td>Source</td>
<td>Study Title</td>
<td>Summary</td>
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<tr>
<td>DeFronzo; Reeves; Awad, 2021.</td>
<td>Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors</td>
<td>Discuss the Physiopathology of diabetic renal disease and the impact of SGLT2 inhibitors. However, because several pathophysiological disorders contribute to the onset and progression of diabetic kidney disease, several agents used in combination are likely to be needed to effectively slow disease progression.</td>
<td></td>
</tr>
<tr>
<td>Rico-Fontalvo et al., 2022.</td>
<td>Molecular Mechanisms of Diabetic Kidney Disease</td>
<td>Explore the different inflammatory mechanisms involved in the pathogenesis of DRD, as well as potential future diagnostic and therapeutic targets. Advances in the knowledge of the pathogenesis of this disease make it clear that one is dealing with a systemic inflammatory condition in which the kidneys are highly affected.</td>
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<tr>
<td>Pena et al., 2022.</td>
<td>Causal relationship between systemic arterial hypertension, diabetes mellitus and chronic kidney disease</td>
<td>Explore the causal relationship between systemic arterial hypertension, diabetes mellitus, and chronic kidney disease. High blood pressure increases intraluminal hydrostatic pressure. Good blood pressure and blood glucose control play a key role in risk reduction and progression of diabetic nephropathy. Amongst the genes associated with this pathology, there is the MMP9, responsible for regulating homeostasis in the renal walls. Alterations in this gene may unleash inflammatory reactions and structural alterations.</td>
<td></td>
</tr>
<tr>
<td>Silva et al., 2023.</td>
<td>MMP9 gene and its association with the development of diabetic nephropathy</td>
<td>Exploring the MMP9 Gene and its association with the development of diabetic nephropathy. Amongst the genes associated with this pathology, there is the MMP9, responsible for regulating homeostasis in the renal walls. Alterations in this gene may unleash inflammatory reactions and structural alterations.</td>
<td></td>
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<tr>
<td>Haber et al., 2023.</td>
<td>Serum creatinine and glomerular filtration rate by equation ckid in children and adolescents with dm1: study observational</td>
<td>Analyze the ratio of serum creatinine and glomerular filtration rate by the CKiD equation with glycaemic control (HbA1c) in children and adolescents with DM1. Elevated eGFR in patients with HbA1c &gt; 8% may suggest an early phase of DRD associated with glomerular hyperfiltration.</td>
<td></td>
</tr>
<tr>
<td>Zhang et al., 2024.</td>
<td>Unveiling the pathogenesis and therapeutic approaches for diabetic nephropathy: insights from panvascular diseases</td>
<td>Further investigate the connection between ND and panvascular diseases. An accuracy-based approach, along with a comprehensive strategy addressing global vascular risk, will be critical to mitigate the cardiorenal burden associated with diabetes.</td>
<td></td>
</tr>
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</table>

Source: own preparation, 2024.
4 DISCUSSION

Diabetic nephropathy is a serious and common complication of diabetes mellitus, characterized by progressive impairment of renal function. It is one of the leading causes of chronic kidney disease and end-stage renal failure worldwide. The development of diabetic nephropathy is closely linked to glycemic control, with chronic hyperglycemia being a crucial factor in the pathogenesis of this condition (Sulaiman, 2019).

According to Maciel, Vasconcelos and Andrade (2019) hyperglycemia, or high blood glucose levels, is the main etiological factor in diabetic nephropathy. Elevated glucose promotes a number of metabolic and haemodynamic changes in the kidneys. The non-enzymatic glycation of proteins resulting from chronic hyperglycemia leads to the formation of advanced glycation products (AGEs), which accumulate in renal tissues and contribute to renal inflammation and fibrosis.

In addition to the formation of AGEs, hyperglycemia causes renal haemodynamic changes, such as glomerular hyperfiltration. Initially, there is an increase in glomerular filtration rate (GFR) due to dilation of afferent arterioles, but over time, this hyperfiltration contributes to mechanical stress on glomeruli, leading to progressive glomerular damage. This process is exacerbated by hypertension, which is common in diabetic patients and additionally contributes to kidney damage (Li et al., 2019).

According to Bommel and his collaborators (2020), intragglomerular hypertension resulting from hyperfiltration leads to damage to endothelial and mesangial cells, in addition to causing thickening of the glomerular basement membrane. These structural changes result in proteinuria, one of the first clinical signs of diabetic nephropathy. The presence of albumin in the urine (microalbuminuria) is often the first detectable indicator of kidney damage in diabetic patients.

Inflammatory and fibrogenic processes also play a significant role in the progression of diabetic nephropathy. Chronic hyperglycemia activates inflammatory signaling pathways, promoting the release of cytokines and growth factors, such as beta-transforming growth factor (TGF-β). This factor contributes to interstitial and glomerular fibrosis, which are striking features of advanced diabetic nephropathy (Wang et al., 2020).

In line with Pugliese and his collaborators (2020) strict glycemic control is critical to slow the progression of diabetic nephropathy. Clinical studies, such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), have shown that maintaining near-normal blood glucose levels significantly reduces the risk of
microvascular complications, including diabetic nephropathy. However, intensive glycaemic control should be balanced with the risk of hypoglycaemia, especially in patients with advanced kidney disease.

In addition to glycaemic control, blood pressure management is crucial in the prevention and treatment of diabetic nephropathy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are often used to reduce intraglomerular pressure and proteinuria, providing additional renal protection. These drugs have beneficial effects beyond lowering blood pressure, including decreasing inflammatory and fibrogenic activity in the kidneys (DeFronzo; Reeves; Awad, 2021).

Rico-Fontalvo and his collaborators (2022) state that early detection and proper management of diabetic nephropathy are essential to prevent progression to end-stage renal failure, which requires dialysis or kidney transplantation. Regular monitoring of renal function, including serum creatinine dosage, estimated glomerular filtration rate (eGFR), and albuminuria, is crucial in diabetic patients for early identification of renal damage.

In addition to medical interventions, lifestyle changes such as a healthy diet, weight control, and regular exercise are important components in managing diabetic nephropathy. These changes help improve glycemic control and blood pressure, and reduce cardiovascular risk, which is high in patients with diabetic nephropathy (Pena et al., 2022).

Finally, Silva and his collaborators (2023) state that diabetic nephropathy is a devastating complication of diabetes mellitus that results mainly from uncontrolled hyperglycemia. Understanding the mechanisms underlying their development and progression, as well as implementing effective glycaemic control and blood pressure strategies, are essential to improve clinical outcomes and quality of life for diabetic patients.

5 FINAL CONSIDERATIONS

Diabetic nephropathy is one of the most severe and debilitating complications of diabetes mellitus, and is a direct consequence of uncontrolled hyperglycemia. Maintaining high blood glucose levels initiates a cascade of pathological events that culminate in progressive kidney damage. The formation of advanced glycation products, hemodynamic changes, and chronic inflammatory processes are the main mechanisms leading to dysfunction and destruction of glomeruli. The development of proteinuria and subsequent loss of renal function underline the importance of early diagnosis and therapeutic intervention to slow disease progression.
Diabetic Nephropathy as a Result of Uncontrolled Hyperglycemia

Strict control of blood glucose and blood pressure, combined with pharmacological interventions and lifestyle modifications, is the basis for effective management of diabetic nephropathy. Therefore, maintaining near-normal blood glucose levels and using inhibitors of the renin-angiotensin-aldosterone system may significantly reduce the progression of nephropathy and improve clinical outcomes. Therefore, the multidisciplinary approach, including patient education, regular monitoring of renal function, and adherence to recommended therapies, is essential to mitigate the devastating effects of chronic hyperglycemia on the kidneys and improve the quality of life of diabetic patients.

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