





Diabetic nephropathy in patients with type 2 diabetes mellitus and its correlation with diabetic retinopathy

Nefropatia diabética em pacientes portadores de diabetes mellitus tipo 2 e sua correlação com a retinopatia diabética

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Abstract

Objective: the present study aimed to evaluate the prevalence of diabetic nephropathy and diabetic retinopathy, in addition to the associations that can be established between these microvascular complications of diabetes mellitus. **Methods:** this was a retrospective study, a systematic review without meta-analysis. The authors used the Pubmed and SciELO databases to search the terms “diabetic nephropathy”, “diabetic retinopathy” and “type 2 diabetes”, including publications dated 2011 to 2021. **Results/Discussion:** the results presented were a synthesis of patients with both pathologies and their correlations, in addition to associated laboratory changes and agreement between the stages or severity of both conditions. **Conclusions:** DN and DR are pathologies that are directly interconnected and cause repercussions for patients.

Keywords: diabetes; diabetic retinopathy; diabetic nephropathy.

Resumo

Objetivo: o presente estudo teve como objetivo avaliar a prevalência de nefropatia diabética e retinopatia diabética, além das associações que podem ser estabelecidas entre essas complicações microvasculares do diabetes mellitus. **Métodos:** estudo retrospectivo, revisão sistemática sem metanálise, os autores utilizaram as bases de dados Pubmed e SciELO para busca dos termos “nefropatia diabética”, “retinopatia diabética” e “diabetes tipo 2”, incluindo publicações datadas de 2011 a 2021. **Resultados/Discussão:** os resultados apresentados foram uma síntese dos pacientes com ambas as patologias e suas correlações, além de alterações laboratoriais associadas e concordância entre os estágios ou gravidade de ambas as condições. **Conclusões:** ND e RD são patologias que estão diretamente interligadas e causam repercussões aos pacientes.

Palavras-chave: diabetes; retinopatia diabética; nefropatia diabética

INTRODUCTION

Diabetes mellitus (DM) is one of the most serious health problems worldwide, reaching epidemic proportions, mainly due to the rapid increase in the global prevalence of type 2 diabetes mellitus (DM2). This chronic condition is associated with a substantial burden of microvascular and macrovascular morbidity, resulting in complications such as diabetic retinopathy (DR), which is the leading cause of blindness in the economically active population in industrialized countries; in addition to diabetic nephropathy (DN), which is the main cause of chronic kidney disease in developed countries, and diabetic polyneuropathy (DPN), which is the main cause of limb amputation^{1,2,3,4}. Furthermore, it has been shown that not only are people diagnosed with diabetes prone to these complications, but studies have also shown that people with prediabetes experience widespread microvascular dysfunction and sequelae that represent end-organ damage typical of diabetes⁵.

Although the etiology of ND, RD and DPN is multifactorial,

involving the magnitude and duration of hyperglycemia and hypertension, in addition to genetic and environmental factors, other determinants that increase the probability or accelerate their development are smoking, obesity, physical inactivity, dyslipidemia, diet rich in fats and carbohydrates. Regarding pathophysiology, DN results from metabolic and hemodynamic impairment, causing inflammation, endothelial dysfunction, oxidative stress, fibrosis, and glomerular hyperfiltration, which lead to kidney damage and potentiate cardiovascular events, which are also related to the pathophysiology of DR, with ND a predictor of DR⁶.

The occurrence of albuminuria is linked to changes that modify glomerular filtration, permeability, and pressure within the renal glomeruli. These changes enabled the filtration of albumin and its excretion through the urine⁷. Recently, a study showed that there was a relationship between ND and albumin excretion in the urine, so there was an approximately five-fold greater risk of developing the disease⁷. It would be important

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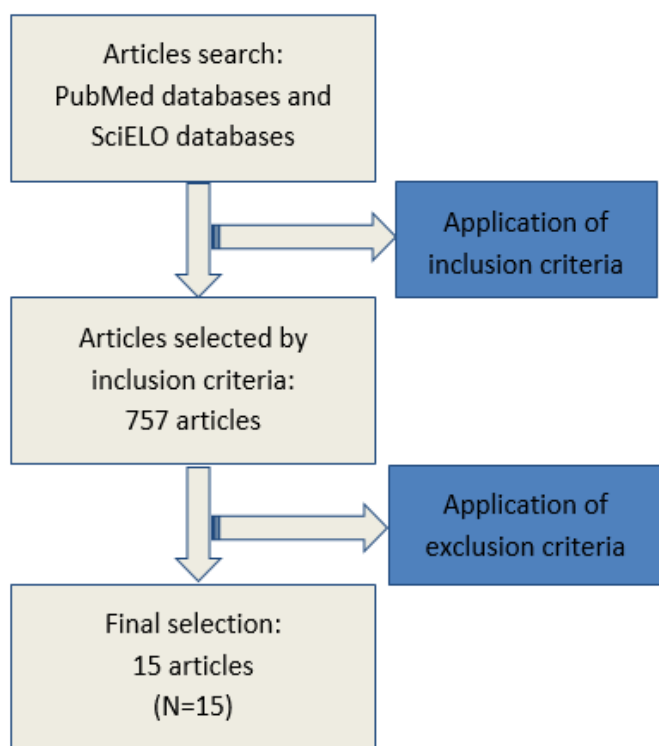
to rule out that kidney injury should be considered a result of DM2 in patients presenting with MA, DR with MA, and urinary protein excretion¹.

Therefore, the objective of this article was to study the prevalence of DN in patients with DM2 and find correlations between ND and RD that could help in patient follow-up.

METHODOLOGY

It was a retrospective study by a systematic review without meta-analysis. The authors used the Pubmed and SciELO databases to search the terms “diabetic nephropathy”, “diabetic retinopathy” and “type 2 diabetes”, including publications dated from 2011 to 2021. The inclusion criteria were clinical trials and randomized clinical trials. Exclusion criteria were reviews, case reports, practice guidelines, letters, overviews, case-control studies, meta-analyses, and cohort studies. After applying these criteria, only articles that correlated DN and RD in patients with DM2 were selected.

Figure 1. Article diagram



Subtitle n = number of articles

RESULTS

Based on what was exposed in the methodology, with the combination of the search terms “diabetic nephropathy and type 2 diabetes”, “diabetic nephropathy and diabetic retinopathy” and “diabetic retinopathy and type 2 diabetes” 5655, 2029, and 4081 articles were found, respectively. After

applying the inclusion criteria, 757 remained, and after applying the exclusion criteria, 15 articles remained.

In the study by Curovic, Viktor Rotbain, et al., a total of 1905 individuals with DM2 were evaluated. These individuals were divided into four (4) groups. In the first group, a total of 203 (26%) had very mild non-proliferative DR, with a diabetes duration of 7.5 years, HbA1c%: 7.93, and 24-hour albuminuria of 5 mg. In the second group, a total of 455 (57%) had mild non-proliferative DR, with diabetes duration of 8.9 years, HbA1c%: 8.17 and 24-hour albuminuria of 5 mg. In the third group, a total of 134 (17%) had severe non-proliferative DR, with diabetes lasting 11.2 years, HbA1c%: 8.51% and 24-hour albuminuria of 6 mg. Urinary peptides, such as collagen alpha-1(I) chain COL1A1 Keratin, type I cytoskeletal 12 KRT12, were also related, in a statistically significant way, to the presence of DR⁶.

In the study by Yijun Zhou, et al., the levels of HbA1c%, albumin, endothelial function markers (VEGF, ET-1, NO) were directly related, with statistical significance, in 100 patients with DM2 and DN and inflammation markers (MCP-1, ICAM, Ptx3)¹.

In the study by Welsh, Paul, et al., 3587 patients with DM2 were evaluated for approximately 3 (three) months, of which 342 had microvascular events, these events being the worsening or appearance of DR or ND. It was identified that high levels of circulating amino acids, tyrosine, and alanine were related to the reduction of these events².

In the study by Nomura, Takuo, et al., 893 men and 549 women with DM2 were investigated. Among men, the prevalence of DR was 14.3%, 26.7% and 61% in the age groups of 30 to 49 years, 50 to 69 years and 70 to 87 years, respectively. Regarding ND, the prevalence was 7.6%, 10.1% and 12.4% for the same age groups, respectively. Among women, the prevalence of DR was 22.2%, 27.8% and 35.6% in the age groups of 30 to 49 years, 50 to 69 years and 70 to 87 years, respectively. Regarding DN, the prevalence was 13.9%, 6.3% and 11.3% for the same age groups, respectively⁶.

The article by Sandbæk, Anelli, et al. demonstrated a relationship between DR and glycated hemoglobin when HbA1c % \geq 6.6. In turn, the study by Hata, Jun, et al. analyzed 8811 people with DM2, of which 755 (9%) had a history of ND and/or DR. This study correlated systolic pressure levels with microvascular events, with the average for this group during the measurement period being 137 mmHg, with a standard deviation of 11, and the maximum levels being 152 mmHg^{3,9}.

It was noted in the article by Heerspink, Hiddo J. Lambers, et al. 2185 people with DM2 and chronic kidney disease with a glomerular filtration rate between 15 and 30 mL/min/1.73m². Patients were divided into three (3) categories according to filtration rate: < 20 mL/min/1.73m², 20 to 25 mL/min/1.73m², and > 25 mL/min/1.73m². The categories had 707, 765, and 713 individuals, respectively, with the prevalence of DR being 45.3%, 40.4%, and 36.7%, respectively. Of the total number of people, 1228 had cardiovascular events, including myocardial

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infarction, coronary angioplasty, hospitalization for unstable angina, hospitalization for heart failure, stroke, transient ischemic attack, and valvular disease, of which 511 (41.6%) had RD¹⁰.

In the article by Chen, Haibing, et al., it was demonstrated that microalbuminuria (MA) in patients with DM2 is related to DR. It was observed that in a sample of 176 people with MA 10.7–30 mg/24 h, 51 (29%) developed DR, while in the sample of 121 people who had MA (<10.7 mg/24 h), only 17 (14.1%) developed DR [7].

The study by Song, Ji Hun, et al. investigated a sample of 116 people with DM2 with an average of 14.8 years of illness. 110 people were observed, and approximately 95% had DR. The average age was 59.5 years. The study by Awata, Takuya, et al. observed that, of a total of 815 people who had DR and DM2, 172 (21%) also had ND, while of a total of 1093 who had DM2 but did not have DR, only 36 (3.3%) had ND^{4,11}.

In the present systematic review, we evaluated the stage and severity of each disease and the interactions between them, so we found risk factors for the development of DN, highlighting genetic susceptibility, systemic arterial hypertension, uncontrolled glycemic levels, obesity and ethnicity [6]. The patients were mostly elderly, aged 60 to 72 years, with stage 1 systemic arterial hypertension with above-normal waist circumference numbers, in addition to high levels of triglycerides and glycated hemoglobin (HbA1c) above 9.2. %⁷, with the habit of smoking cigarettes. Therefore, a direct relationship was established between the pathologies of this study and metabolic syndrome so that peripheral insulin resistance was a common point between the three variables³.

Laboratory parameters were used to diagnose both diseases,

in this context, albumin stood out mainly. A relationship was established between albumin levels and DR, so in the study by Chen, Haibing, et al. there were diabetic patients with normal levels, low levels and high levels of albumin. However, most patients with DR had high levels of albumin⁷.

As DN is a disease that initially affects microcirculation, DR would be a complication that appears early on and would also be the most common. There would be increased expression of VEGF, which could promote angiogenesis and cause glomerular hyperfiltration; however, when in the late phase of the disease, there would be a decrease in VEGF, resulting in fewer capillaries and, consequently, a lower glomerular filtration rate, in addition of a smaller number of capillary glomeruli¹.

From what was exposed, it became clear that DN and DR are pathologies that are interconnected as they have an intimate cause-effect relationship; therefore, everything from risk factors to laboratory changes has points in common between both pathologies. Insulin resistance and, consequently, sustained hyperglycemia are pillars for the development and progression of diseases¹.

It is known that patients affected by DN can potentially develop DR, depending on the degree of renal involvement, notably one of the first microvascular complications to develop, leading to loss of vision and, in some cases, causing blindness. Therefore, the prevalence number of patients with DN presents an equal relationship with patients with DR⁶.

It is essential to highlight the importance that the renal system has in all pathophysiology so that glomerular filtration is a determinant of the severity of pathologies. Furthermore, albumin is an important marker, so both patients have high levels of urinary excretion of the protein⁷.

Table 1. Main conclusions from the results.

Authors	Findings
Welsh, Paul, et al.	It was identified that high levels of circulating amino acids, tyrosine, and alanine were related to the reduction of microvascular events
Nomura, Takuo, et al.	The prevalence of DR and ND is higher in elderly men
Heerspink, Hidjo J. Lambers, et al.	The prevalence of RD is higher in DM2 patients with chronic kidney disease with a glomerular filtration rate between 15 and 30 mL/min/1.73m ² and systemic arterial hypertension
Chen, Haibing, et al.	Microalbuminuria in patients with DM2 is related to DR
Sandbæk A, Griffin SJ, et al.	It was identified risk factors for the development of DN, highlighting genetic susceptibility, systemic arterial hypertension, uncontrolled glycemic levels, obesity and ethnicity
Curovic VR, et al.	Therefore, a direct relationship was established between the pathologies of this study and metabolic syndrome so that peripheral insulin resistance was a common point between the three variables
Chen H, Zheng Z, Huang Y, et al.	Most patients with DR had high levels of albumin
Yijun Zhou, et al.	DR would be a complication that appears early on and would also be the most common
Yijun Zhou, et al.	Insulin resistance and, consequently, sustained hyperglycemia are pillars for the development and progression of diseases
Chen H, Zheng Z, Huang Y, et al.	Albumin is an important marker, so both patients have high levels of urinary excretion of the protein

CONCLUSION

Finally, DN and DR are pathologies that are directly interconnected and cause repercussions that interfere with the

quality of life of affected patients.

REFERENCES

1. Yijun Zhou, Qi C, Li S, Shao X, Mou S, Ni Z. Diabetic Nephropathy Can Be Treated with Calcium Dobesilate by Alleviating the Chronic Inflammatory State and Improving Endothelial Cell Function. *Cell Physiol Biochem*. 2018; 51(3): 1119–1133. doi: 10.1159/000495491.
2. Welsh, P, Rankin N, Li Q, Mark PB, Würtz P, Ala-Korpela M, et al. Circulating amino acids and the risk of macrovascular, microvascular and mortality outcomes in individuals with type 2 diabetes: results from the ADVANCE trial. *Diabetologia*. 2018 Jul; 61(7): 1581–1591. doi: 10.1007/s00125-018-4619-x.
3. Sandbæk A, Griffin SJ, Sharp SJ, Simmons RK, Borch-Johnsen K, Rutten GE, et al. Effect of Early Multifactorial Therapy Compared With Routine Care on Microvascular Outcomes at 5 Years in People With Screen-Detected Diabetes: A Randomized Controlled Trial: The ADDITION-Europe Study. *Diabetes Care*. 2014 Jul; 37(7): 2015–2023. doi: 10.2337/dc13-1544.
4. Song JH, Chin HS, Kwon OW, Lim SJ, Kim HK, DRESS Research Group. Effect of sulodexide in patients with non-proliferative diabetic retinopathy: diabetic retinopathy sulodexide study (DRESS). *Graefes Arch Clin Exp Ophthalmol*. 2015 Jun; 253(6): 829–37. doi: 10.1007/s00417-014-2746-8.
5. Gabriel R, Abdelkader NB, Acosta T, Gils-Januszewska A, Gómez-Huelgas R, Makrilakis K, et al. Early prevention of diabetes microvascular complications in people with hyperglycaemia in Europe. ePREDICE randomized trial. Study protocol, recruitment and selected baseline data. *Plos One*. 2020 Apr; 15(4): e0231196. doi: 10.1371/journal.pone.0231196.
6. Curovic VR, Magalhães P, He T, Hansen TW, Mischak H, Rossing P, et al. Urinary peptidome and diabetic retinopathy in the DIRECT-Protect 1 and 2 trials. *Diabet Med*, 2021 Sep; 38(9): e14634. doi: 10.1111/dme.14634.
7. Chen H, Zheng Z, Huang Y, et al. A microalbuminuria threshold to predict the risk for the development of diabetic retinopathy in type 2 diabetes mellitus patients. *PLoS One*. 2012; 7(5): e36718. doi:10.1371/journal.pone.0036718.
8. Nomura, T, Ishiguro, Ohira M, Ikeda Y. Diabetic polyneuropathy is a risk factor for decline of lower extremity strength in patients with type 2 diabetes. *J Diabetes Investig*. 2018 Jan; 9(1): 186–192. doi: 10.1111/jdi.12658.
9. Hata J, Arima H, Rothwell PM, Woodward M, Zoungas S, Anderson C, et al. Effects of Visit-to-Visit Variability in Systolic Blood Pressure on Macrovascular and Microvascular Complications in Patients With Type 2 Diabetes Mellitus The ADVANCE Trial. *Circulation*. 2013 Sep; 128(12): 1325–1334. doi: 10.1161/CIRCULATIONAHA.113.002717.
10. Heerspink HJL, Chertow GM, Akizawa T, Audhya P, Bakris GL, Goldsberry A, et al. Baseline characteristics in the Bardoxolone methyl Evaluation in patients with Chronic kidney disease and type 2 diabetes mellitus: the Occurrence of renal events (BEACON) trial. *Nephrol Dial Transplant*. 2013 Nov; 28(11): 2841–2850. doi: 10.1093/ndt/gft445.
11. Awata T, Yamashita H, Kurihara S, Morita-Ohkubo T, Miyashita Y, Katayama S. A Genome-Wide Association Study for Diabetic Retinopathy in a Japanese Population: Potential Association with a Long Intergenic Non-Coding RNA. *Plos One*. 2014 Nov; 9(11): e111715. doi: 10.1371/journal.pone.0111715.
12. Tryggestad, Jeanie B, Shah RD, Braffett BH, Bacha F, Gidding SS, et al. Circulating adhesion molecules and associations with HbA1c, hypertension, nephropathy, and retinopathy in the Treatment Options for type 2 Diabetes in Adolescent and Youth study. *Pediatr Diabetes*. 2020 Sep; 21(6): 923–931. doi: 10.1111/pedi.13062.
13. Kukidome D, Nishika T, Sato M, Igata M, Kawashima J, Shimoda S, et al. Measurement of small fibre pain threshold values for the early detection of diabetic polyneuropathy. *Diabet Med*. 2016 Jan; 33(1): 62–69. doi: 10.1111/dme.12797.
14. Briguori C, Airolò F, Visconti G, Focaccio A, Caiazzo G, Golia B, et al. Novel Approaches for Preventing or Limiting Events in Diabetic Patients (Naples-Diabetes) Trial. *Cir Cardiovasc Interv*. 2011 Apr; 4(2): 121–129. doi: 10.1161/CIRCINTERVENTIONS.110.959924.
15. Lu M, Zhang J, Li M, Ge X, Dai X, Zhao J, Fu M, et al. The angiotensin-I converting enzyme gene I/D variation contributes to end-stage renal disease risk in Chinese patients with type 2 diabetes receiving hemodialysis. *Mol Cell Biochem*. 2016 Nov; 422 (1-2): 181–188. doi: 10.1007/s11010-016-2819-6.

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