sciendo Acta Marisiensis - Seria Medica 2023;69(3):176-181 DOI: 10.2478/amma-2023-0024

RESEARCH ARTICLE

Correlation between diabetic nephropathy and diabetic retinopathy as a long term complications of diabetes mellitus

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Background/aim: Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by a lack of insulin, with a consequent disordered metabolism of glucose, fats, and proteins. A number of complications, such as diabetic nephropathy and retinopathy, may develop as a result of long-term diabetes. The aim of this study aimed to determine the correlation between diabetic nephropathy and diabetic retinopathy as long-term complications of diabetes mellitus. **Materials and methods**: Retrospective, descriptive, and analytical research was conducted at the department of Endocrinology, Clinical Center, University of Sarajevo. The study included 158 patients hospitalized in time between 1st of January and 31st of December 2012. **Results**: New-onset diabetes was found in 38%, and diabetes type 2 patients 132 (83.5%), female 105 (66.5%) while older than 60 years were 100 (63.3%). Upon discharge from hospital 83,7% of patients were discharged with glycemia <10 mmol / l. We found that 47,5% of patients had HbA1c> 10%. Reduced kidney function, different degrees of failure was at 66.5%. More than half (62.7%) patients had proteinuria as a sign of diabetic nephropathy. Diabetic retinopathy was diagnosed with different types in 54.4%. **Conclusion**: Diabetes leads to an increase in nitrogen compounds, and the development of diabetic nephropathy manifests as various degrees of renal insufficiency. The duration of diabetes and occurrence of diabetic retinopathy were significantly interrelated. The correlation between the degree of renal failure and changes in the ocular fundus has not been proven, but more severe renal insufficiency is associated with a higher incidence of diabetic retinopathy compared to patients with less impaired renal function.

Keywords: diabetes mellitus, microvascular, retinopathy, diabetic nephropathy

Received 6 March 2023 / Accepted 21 May 2023

Introduction

Diabetes mellitus (DM) is a group of metabolic disorders caused by complex interactions between modifiable and immutable risk factors [1]. There are two categories of DM. Type 1 DM results from autoimmunity to pancreatic beta cells, resulting in partial or complete insulin deficiency, while type 2 DM represents a heterogeneous group of disorders characterized by varying degrees of insulin resistance, hyperproduction of glucose in the liver, or impaired insulin secretion.

Complications associated with diabetes can be divided into vascular (microvascular, nephropathy, retinopathy, and neuropathy; macrovascular, coronary disease, arterial disease, and cerebrovascular) and non-vascular complications (infections, hearing loss, and skin changes). Recent research shows that DM type 2 increases the risk of dementia and cognitive dysfunction [2].

It is estimated that DM affects 7.2–11.4% of the world's population [3,4]. According to data from the World Health Organization (WHO), diabetic retinopathy (DR) is responsible for 3–7% of total blindness in Asia [5] and in India for about 3.5% [6]. Considering the multifactorial nature of DM (duration of DM, glycemic control, age, dyslipidemia, anemia, nicotine, and alcohol consumption), monitoring is possible as a predictor for the development of retinopathy [7,8].

Diabetic nephropathy (DN) is a clinical syndrome that includes low glomerular filtration rate (GFR), hypertension, and proteinuria [9]. Generally, 25-45% of patients with DM type 1 develop nephropathy, on average, between 10 and 15 years from the onset of the disease [10]. Nephropathy develops in approximately 50% of type 2 DM patients [11].

Diabetes and uncontrolled hyperglycemia play a significant role in the development of long-term complications, such as diabetic nephropathy and retinopathy.

The aim of this study was to determine the correlation between diabetic nephropathy and diabetic retinopathy as long-term complications of diabetes mellitus

Methods

This retrospective study was conducted in the Department of Endocrinology, University Clinical Center of Sarajevo, which lasted one year (2012). This study included 158 case histories that started in the same year, distributed in two group of patients: newly diagnosed diabetics and confirmed diabetics. The study protocol was approved by the Ethics Committee of University Clinical Center (approval no:01-4-TK-1150/13). This study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

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Exclusion criteria

A newly diagnosed diabetics and confirmed diabetics lasting less than a year were excluded from the study. Patients with cancer, pregnancy, other autoimmune diseases, or a history of ocular inflammation or ocular trauma were excluded.

Inclusion criteria and collecting data

We used the following data by examining the medical histories:

- Anamnesis data, which included age, sex (m/f), duration of diabetes, type of diabetes (type 1, type 2), and type of diabetes therapy at admission
- Clinical examination: Blood pressure
- Laboratory tests: glycemic values at admission and discharge; HbA1c value (reference value: 6.0 - 7.0 %); urea in the blood (reference value: 2 - 7.8 mmol/l); creatinine in the blood (reference value: 45 - 115 μmol/l); creatinine clearance (reference value: 1.4 - 2.7 ml/s); proteinuria / in 24h urine (normal up to 0.20 g/day); Gradation of renal insufficiency in diabetic nephropathy according to creatinine clearance values
- Morphological diagnostics: Examination of the fundus of the eye (I: Normal examination, without visible pathological changes; II: Retinopathy diabetica incipientis (non-proliferative); III: Diabetic retinopathy pre-proliferative; IV: Retinopathy diabetic proliferative)

Results

Data were retrospectively analyzed from 158 patients with diabetes within one year. 83.5% were DMT2, and 16.5% were DMT1.

The largest number were newly diagnosed diabetes and those with diabetes less than five years 38%, while the smallest number of respondents had diabetes between 16 and 20 years of 8.9% (Table 1).

The largest number of patients at discharge had a value of blood glucose <10 mmol/l (87.3%), and the smallest number of respondents and 12.7% of them had blood glucose values from 10.1 to 15.0 mmol / l (Table 2).

HbA1c values> 10% were in 47.5% patients. HbA1c from 8.1 to 10% were in 25.3% patients, while 14.6% of respondents were with HbA1c values between 7.1 to 8%. Optimum control HbA1c values from 6.0 to 7.0 mmol / l, there were in 12.7% patients (Table 3).

62.7% patients had proteinuria above the reference value, while 37.3% patients had proteinuria within the reference value (Table 4).

The largest number of respondents, 45.6% had normal findings in fundus, while the smallest number of respondents had pre-proliferative diabetic retinopathy, 10.8% of them. Incipient retinopathy had 30.4% of patients, while 13.3% of patients had a finding of proliferative diabetic retinopathy (Table 5).

Most of the patients had a stage II renal failure, 35.4% of patients, while the 1.9% patients had fourth (IV) stage of renal failure (insufficiency). The fifth (V) stage of renal failure was not verified in one of the tested patients. The first (I) stage of renal failure had 27.8% patients and normal renal function 28.5% of patients (Table 6).

A comparison between renal failure and retinopathy indicated that normal renal function and renal impairment level IV were more common in patients with retinopathy,

Table 1. Duration of diabetes

Duration of diabetes (year)	N	%	Cumulative %
Newly diagnosed - < 5	60	38.0	38.0
6-10	35	22.2	60.1
11-15	31	19.6	79,7
16-20	14	8.9	88.6
>20	18	11.4	100.0
Total	158	100.0	

Table 2. Blood sugar values

Fasting glucose (mmol/L)	N	%	Cumulative %
<10	138	87.3	87.3
10.1-15.0	20	12.7	100.0
Total	158	100.0	

Table 3. HbA1c values

HbA_{1c} (%)	N	%	Cumulative %
6.0-7.0%	20	12.7	12.7
7.1-8.0%	23	14.6	27.2
8.1-10%	40	25.3	52.5
> 10%	75	47.5	100.0
Total	158	100.0	

Table 4. Values of proteinuira 24/h

Proteinuria/24h (g/l)	N	%	Cumulative %
<=0,20 g/l	59	3.3	37.3
>0,20 g/l	99	62.7	100.0
Total	158	100.0	

Table 5. Diabetic retinopathy classification

Fundus changes	N	%	Cumulative %
Regular (no diabetic retinopathy)	72	45.6	4.6
Mild (Retinopathia diabetica incipientis)	48	30.4	75.9
Moderate (Retinopathia diabetica praeproliferativa)	17	10.8	86.7
Severe (Retinopathia diabetica proliferativa)	21	13.3	100.0
Total	158	100.0	

Table 6. The stage of renal failure

The stage of renal failure	N	%	Cumulative %
Normal renal function	45	28.5	28.5
I stage of renal failure	44	27.8	56.3
II stage of renal failure	56	35.4	91.8
III stage of renal failure	10	6.3	98.1
IV stage of renal failure	3	1.9	100.0
V stage of renal insufficiency	0	0	0
Total	158	100.0	

and other stages (I, II, and III) showed no changes in the fundus of the eye. Diabetics with criteria for stage V renal failure were not included. Statistical analysis by the chi-square test showed that there was no statistical difference in the significant groups classified according to the stages of renal failure (p> 0.05). Spearman's correlation analysis indicated that there was no significant correlation between the stages of renal failure and the presence of diabetic retinopathy (p> 0.05) (Figure 1).

Analysis of the correlation between the duration of diabetes and creatinine values through Pearson correlation coefficient showed that there was a positive correlation that was not statistically significant; however, a longer duration of diabetes led to slight elevations in serum creatinine (p> 0.05) (Figure 2).

Analysis of the correlation between the duration of diabetes and retinopathy by Spearman's correlation coefficient showed that there was a statistically significant positive correlation. A longer duration of diabetes led to frequent occurrence of the fundus of the eye (p <0.05) (Figure 3).

Analysis of the correlation between HbA1c and serum creatinine via the Pearson correlation coefficient showed

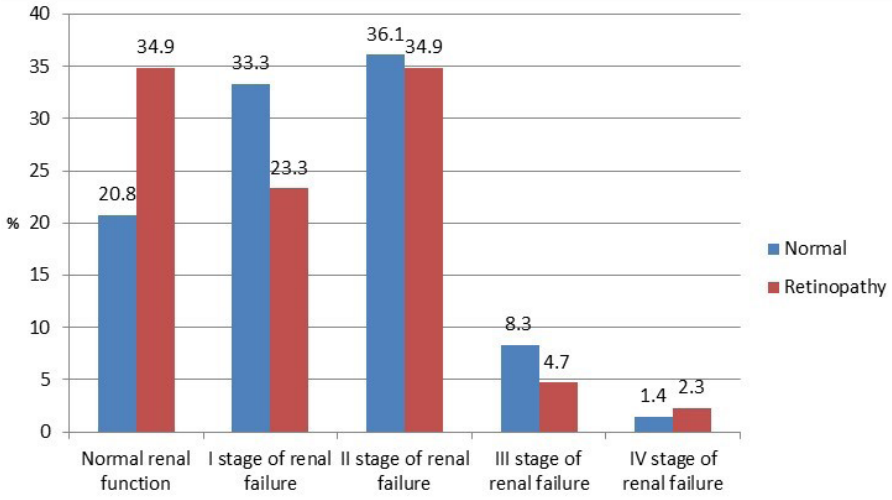
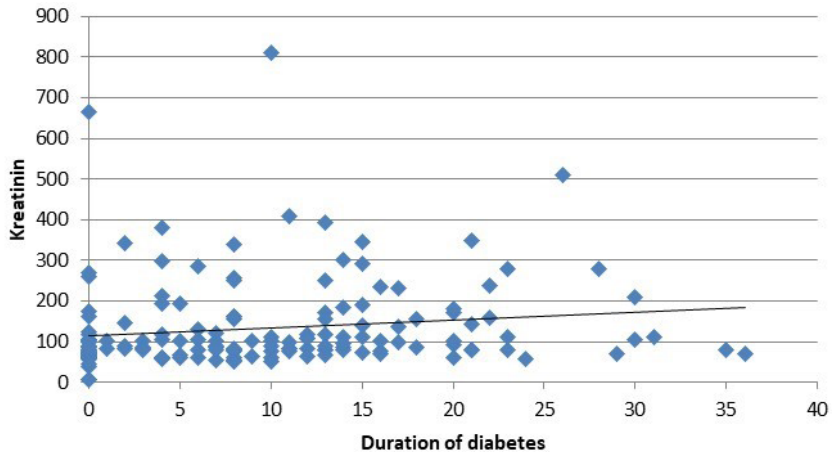


Fig. 1. Correlation between renal failue and Retinopathy



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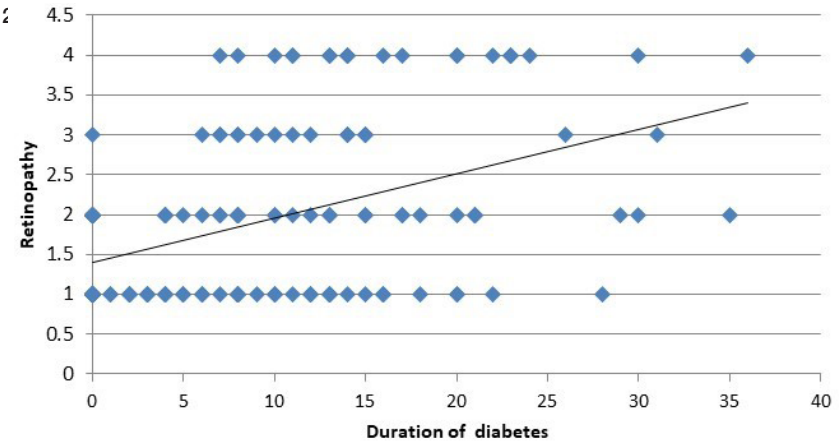

Fig. 3. The correlation coefficient between the duration of diabetes and retinopathy

that there was no statistically significant correlation (Figure 4).

Analysis of the correlation between HbA1c and retinopathy by Spearman's correlation coefficient showed that there was no statistically significant correlation (Figure 5).

Discussion

Secondary pathophysiological systemic changes caused by metabolic imbalance as part of diabetes mellitus impose a great burden on both the affected person and his family, as well as the health system [1]. The primary aim of this study was to determine the correlation between retinopathy and nephropathy in patients with DM.

In our study, the largest number of patients was older than 60 years, and the smallest number of patients was between 41 and 50 years. Many studies have shown that the incidence of diabetes increases with age, which is consistent with our results [1]. Out of 158 patients, it was represented in a significantly higher percentage female population (66.5% vs. 33.5%).

The value of glycosylated hemoglobin (HbA1c) reflected the average glycemia during the past

4 months. For most DM patients, the target HbA1c level was <6%. As far back as 1998, there has been a high trend of studies examining microvascular complications of diabetes in target groups and the association of microvascular complications with elevated values of glycosylated hemoglobin [12]. In our study, according to HbA1c values, it was determined that a large percentage of patients had unregulated glycemia, with HbA1c >10% (47.5%), while only 12.7% had HbA1c in the range of 6.0 – 7.0% (12.7%)

Diabetes mellitus is one of the most common individual causes of terminal renal insufficiency in the USA and Europe, and this is primarily due to the fact that diabetes, especially type 2, is on the rise, and that patients with diabetes now have a significantly longer life expectancy. About 20-30% of patients with type 1 and type 2 diabetes develop manifest nephropathy, but the number of patients is much smaller, who develop terminal stage chronic renal insufficiency. A reduction in creatinine clearance below 15 ml/min indicates the onset of the terminal phase of renal insufficiency with signs of uremic syndrome. End-stage renal failure develops within 10 years in 50% of patients with diabetic nephropathy [13]. Several studies have shown that the duration of diabetes and the occurrence of nephropathy are significantly related in the post-puberty period and that there is no connection between the duration of diabe-

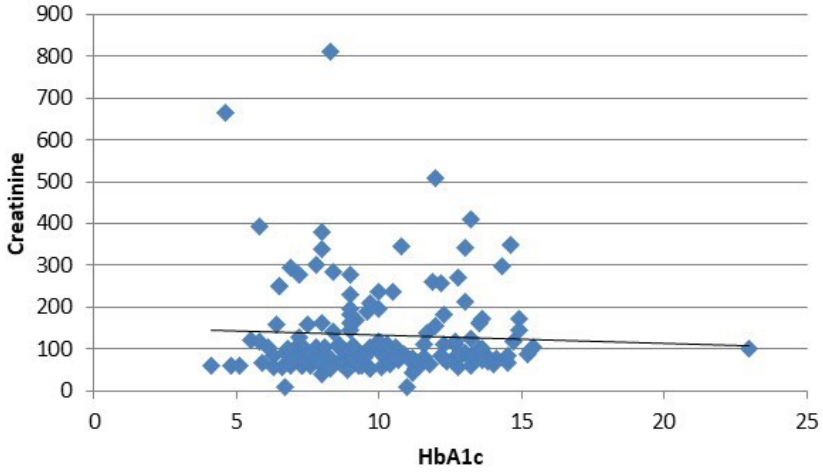

Fig. 4. The correlation coefficient between HbA1c and serum creatinine values

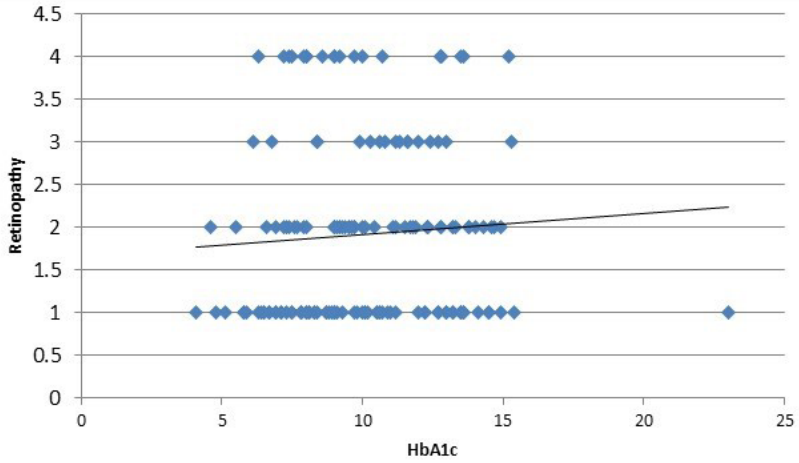

Fig. 5. The correlation coefficient between HbA1c and retinopathy

tes before puberty and the onset of microalbuminuria and nephropathy [2]. Such a connection was not confirmed by the results of the study International Diabetic Nephropathy Study (IDNS), where 243 young patients with diabetes found that total time is important for the development of diabetic nephropathy duration of diabetes (and not only the post-puberty period). In the available literature, studies have found in which the cumulative frequency of microalbuminuria in DM type 1 was 12% over a period of 7 years of follow-up [14,15]. When it comes to DM type 2 patients, the frequency of microalbuminuria is 2% per year, and after 10 years of disease duration, the prevalence of microalbuminuria is 25% [16].

Trials and the diversity of results should be seen in the light of the results of recent studies that show that 30% of microalbuminuria regresses spontaneously, and 20% progresses to nephropathy in period from 5 to 9 years.

From the total number of our patients (n=158), the largest number of patients (35.4%) had II degree of renal insufficiency, while the smallest number (1.9%) of patients had IV degree renal insufficiency. Stage V renal insufficiency was not observed in any of them examined patient. 27.8% patients had a first degree of renal insufficiency, a normal kidney function 28.5% patients.

Diabetic retinopathy (DR) is a characteristic vascular complication of diabetes mellitus. Considers cause more than 10,000 blind diabetics [17]. Results of the Wisconsin study Epidemiologic Study of Diabetic Retinopathy (WESDR) show that 3.6% of patients with are blind from diabetes, and that diabetic retinopathy is the cause of 86% of cases of blindness [18,19]. In our study, out of the total number of patients, the largest number 45.6% of them had a normal finding of the fundus, while the smallest number of patients (10.8%) had pre-proliferative diabetic retinopathy, 30.4% of them had incipient retinopathy, and 13.3% patients were diagnosed with proliferative diabetic retinopathy. Various epidemiological studies have shown a significant association diabetic retinopathy and microalbuminuria and diabetic nephropathy [20]. The development of diabetic retinopathy is positively correlated with clinical signs of diabetes nephropathy [20]. The authors found a concurrent prevalence of retinopathy in 23% and nephropathy in 22% of cases [20].

A statistically significant positive correlation was established, that is, yes with a longer duration of diabetes, there were more frequent occurrences on the fundus ($p<0.05$).

A prospective study (Prospective Diabetes Study-UKPDS) was conducted in Great Britain, where it was established that the development of diabetic retinopathy in patients with type 2 diabetes is related to the level of glycemia and the presence of hypertension, whereas most patients with type 1 diabetes develop retinopathy for an average of 20 years from the first diagnosis of diabetes [21].

In our study, comparing the degree of renal function impairment according to the presence of diabetic retinopathy, we found that the degree of renal insufficiency was more common in patients with retinopathy and other degrees of renal weakness (I, II, and III) with normal fundus findings in the eye. Such results could indicate that retinopathy occurs in advanced developmental stages of renal weakness, while individual retinopathy can also occur with normal kidney function. We did not find a statistically significant difference between the degree of renal insufficiency and presence of diabetic retinopathy ($p=0.052$).

The test results showed no statistically significant correlation between HbA1c as a marker of adequate glycemic control and changes in the fundus; thus, with changes in HbA1c values, there were no major changes in the fundus of the eye ($p>0.05$).

In a study by Nakayoshi et al. Give the results that include the level of fasting glycemia and HbA1c in a positive correlation with the severity and progression of diabetes retinopathy, while in study by Vilsbøll T et al. [22] did not find a positive correlation between diabetic retinopathy and HbA1c level. Until 2022, there was no gold standard for the diagnosis of diabetic retinopathy, but glycosylated hemoglobin is one of the best predictors for the eventual development of diabetic retinopathy.

In our analysis, we made a correlation between patients with diabetic nephropathy, with normal and damaged kidney function in relation to the presence or absence diabetic retinopathy. We found that these complications are not related to each other and that patients who have verified diabetic retinopathy do not have to develop renal weakness caused by diabetic nephropathy. The mechanism of pathogenesis of retinopathy and nephropathy, as microvascular complications of diabetes, is almost the same, so the course of development and complications are closely or marginally related. Therefore, in our study, the increasing severity of retinopathy was closely related to the increasing severity of diabetic nephropathy. Similar findings were reported in some studies in which 20.50% of patients with diabetes for less than 5 years had microalbuminuria, while in patients with diabetes for more than 15 years, 90% had microalbuminuria [23-25]. A multiple increase was also observed in the microvascular complication of retinopathy, which in patients with diabetes duration of less than 5 years amounted to 25.6%, whereas in patients with diabetes duration of more than 15 years, it resulted in a 100% diagnosis of retinopathy.

Conclusion

No correlation was observed between the degree of renal weakness and changes in the eye fundus.

However, patients with more severe forms of renal insufficiency have a more frequent presence of diabetic retinopathy compared to patients with less impaired renal function. By correlating renal insufficiency and changes in the fundus, it was determined that these complications of diabetic disease develop independently.

This study had certain limitations. First, the sample of one year was small for evaluation, and in the next study,

we should go towards larger databases and more numerous laboratory parameters and indicators of complications of diabetes.

Author contributions

MD - Investigation; Methodology; Resources
DR - Software; Writing; Analysis; Editing
ED - Supervision; Writing original draft; Data curation

Acknowledgment/conflict of interest

The authors declare no conflicts of interest.

Informed consent

Approval was obtained from the ethics committee, and the date of approval was May 2013. The study protocol was approved by the Ethics Committee of University Clinical Center (approval no:01-4-TK-1150/13). This study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013. Informed consent was obtained from all the participants.

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