International Journal of Advances in Medicine
Mohan C et al. Int J Adv Med. 2020 Jan;7(1):17-21
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20195568

Original Research Article

Association of diabetic nephropathy with diabetic retinopathy in type 2 diabetes mellitus patients

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Received: 18 November 2019
Accepted: 27 November 2019

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ABSTRACT

Background: Microvascular complications of Type 2 Diabetes Mellitus (T2DM), (retinopathy and nephropathy) have a similar etiopathogenetic mechanism besides genetic predisposition. Even though these two complications frequently co-exist, their frequency varies. The association of these two significant complications and their co-existence needs a relook.
Methods: Four hundred patients suffering from type 2 DM visiting a tertiary care hospital in Western India were included in this cross-sectional study. Of these, 200 patients were of Diabetic Nephropathy (DN) and 200 were without DN. The presence of albuminuria (urine albumin-creatinine ratio) was used to detect diabetic nephropathy. Fundoscopy was performed in all patients to look for Diabetic Retinopathy (DR).
Results: In this study, 77.5% patients with DN had retinopathy, while in patients without DN, only 52% patients had retinopathy. This was a statistically significant finding. (p value <0.001). The distribution of types of retinopathy in patients with DN was 63.0% Non-Proliferative Diabetic Retinopathy (NPDR), 12.5% Proliferative Diabetic Retinopathy (PDR) and 2% Clinically Significant Macular Edema (CSME). While in those without DN, 50.5% had NPDR, 1.5% had PDR and none had macular edema.
Conclusions: Microalbuminuria, which has been used so far to diagnose DN, may be considered as a reliable predicter of diabetic retinopathy in type 2 diabetes mellitus patients. This simple marker can help screen all patients with Diabetes for nephropathy and retinopathy both and should take place at the first visit/ contact of the healthcare personnel. This can help prevent microvascular complications early and help in goal directed therapy.

Keywords: Diabetic nephropathy, Diabetic retinopathy, Type 2 diabetes mellitus

INTRODUCTION

The prevalence of diabetes mellitus has been increasing globally and India now stands next only to China in terms of absolute numbers. This has also resulted in a parallel increase in the macrovascular and microvascular complications of Diabetes which imposes a huge burden on the health care services of the country.[1-3]

Microvascular complications of type 2 Diabetes Mellitus-Nephropathy and Retinopathy have similar etiopathogenetic mechanisms. These two complications frequently co-exist; however, the frequency varies. These complications Diabetic Nephropathy and Diabetic Retinopathy (DN and DR) can have severe consequences on health which may eventually lead to end-stage renal disease and blindness respectively. With changing treatment targets, age profile, new drugs, and patient awareness of type 2 DM, the frequency of co-existence of these two significant complications needs a relook. Population-based epidemiological studies have shown that patients with DN experienced higher incidence of

DR as compared to patients without DN.[4,5] However, data from hospital settings regarding similar reports is sparse. Hence, this study aims to determine the association between DR and DN, in patients with type 2 DM presenting to a tertiary care centre.

METHODS

This is a cross-sectional hospital-based study conducted in the Department of Medicine at a tertiary care centre in western India from July 2017-Jun 2018. Sample size was 400 patients of type 2 DM, out of which 200 patients with DN and 200 patients without DN were included. Diabetes Mellitus was diagnosed as per standard guidelines of American Diabetes Association (ADA) Guidelines.[6] Pregnant women, patients having Urinary Tract Infection (UTI), fever, renal calculi, heart failure or any other condition confounding proteinuria were excluded.

Diabetic nephropathy was diagnosed based on the presence of albuminuria (microalbuminuria defined as urine albumin-creatinine ratio of 30-299 mg/g Cr or macroalbuminuria defined as albumin-creatinine ratio ≥300 mg/g Cr) and/or reduced estimated Glomerular Filtration Rate (eGFR) <90 ml/min/m^2.[7] For this, spot urine sample was obtained for estimating urine albumin-creatinine ratio and the samples were freshly analyzed on the same day (Siemens Dimension ® EXL ™ 200 Integrated Chemistry System).

A written informed consent was obtained from the study participants and patients fulfilling the inclusion criteria were taken for further evaluation. The Ethics Committee approval was taken before the start of the study. Data (including duration of the disease, presence of other co-morbidities, risk factors and treatment) was obtained after patient interview and accessing available respective OPD records/ case sheets. For calculation of BMI, height was measured using Harpenden's stadiometer and weight was obtained from a digital weighing scale (average of 3 readings taken). Blood pressure was determined clinically by digital blood pressure apparatus (OMRON).

The patients underwent fundoscopic examination using a standard ophthalmoscope. Based on fundoscopy, patients were further classified into Non-Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR) and those having Clinically Significant Macular Edema (CSME) as per Early Treatment Diabetic Retinopathy Study (ETDRS) classification.[8]

The data on categorical variables was represented as frequency and percentages. The data on continuous variables was presented as Mean and Standard Deviation (SD) across the two study groups. The inter-group comparison of categorical variables was done using Chi-square test or Fisher's exact probability test. The statistical significance of continuous variables was tested using independent sample t test or unpaired t test. In the entire study, the p-values less than 0.001 were considered statistically significant. The entire data was analyzed using Statistical Package for Social Sciences (SPSS version 23.0, IBM Corporation, USA) for MS Windows.

RESULTS

Four hundred patients of type 2 diabetes mellitus were evaluated. In patients with DN, the gender ratio of males to females was 119: 81 and in patients without DN, the ratio was 129 :71. The mean age of patients with DN was 68.4±4.46 years and in those without DN, it was 66.62±4.2 years. The mean duration of Diabetes was 8.34±3.33 years in the patients with DN and 7.34±2.61 years in those without DN which was statistically significant (p-value <0.001). It was also observed that the eGFR values were significantly low among the patients with DN when compared to those without DN (p<0.001) (Table 1).

Table 1: Demographics and comorbidities of type 2 diabetes mellitus patients with and without Diabetic Nephropathy (DN).

Parameter	Patients with DN (n=200)	Patients without DN (n=200)	p value
Age (in years)	68.4±4.46	66.62±4.2	<0.001
Sex (M: F)	129:71	119:81	0.303
Duration of disease (yrs.)	8.34±3.33	7.34±2.61	<0.001
BMI (kg/m^2)	25.59±2.24	25.65±2.78	0.819
HbA1c (%)	8.82±0.79	8.61±0.77	<0.001
eGFR (ml/min/m^2)	34.71±12.62	54.91±10.89	<0.001
Co-morbidities			
Hypertension	50.5%	40.5%	<0.001
CAD	10.5%	7%	<0.001
Dyslipidemia	7%	5%	<0.001
Obesity	8.5%	12.5%	0.045

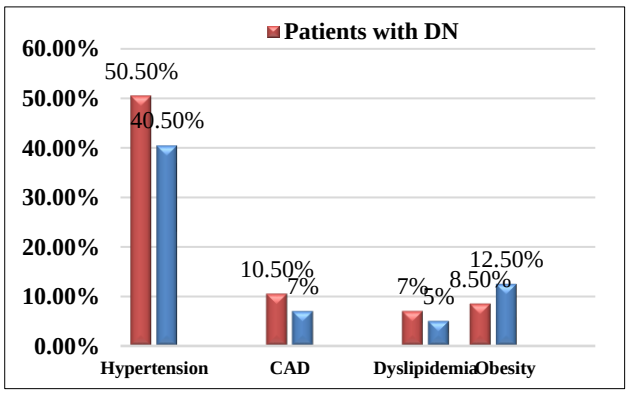

Figure 1: Comorbidities in patients with and without diabetic nephropathy.

The study showed that comorbidities like HT, CAD and dyslipidemia were common in patients with DN as

compared to those without DN (50.5% vs 40.5%, 10.5% vs 7% and 7% vs 5% respectively) (Figure 1). The prevalence of obesity was 8.5% in individuals with DN and 12.5% without DN. However, this was not statistically significant.

The proportion of patients with retinopathy was significantly higher in patients of DN as compared to those without DN (Figure 2 and 3). Out of 200 individuals with DN, 77.5% had retinopathy while only 52% had retinopathy in those without DN. This was statistically significant. (p<0.001) (Table 2).

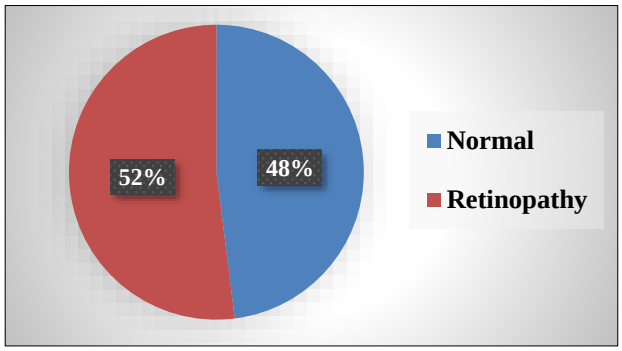

Figure 2: Distribution of diabetic retinopathy in patients without nephropathy.

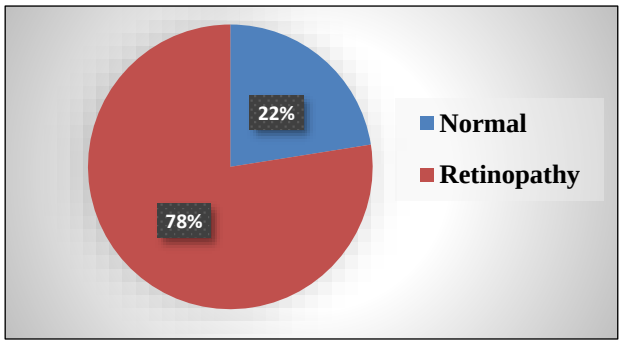

Figure 3: Distribution of diabetic retinopathy in patients with nephropathy.

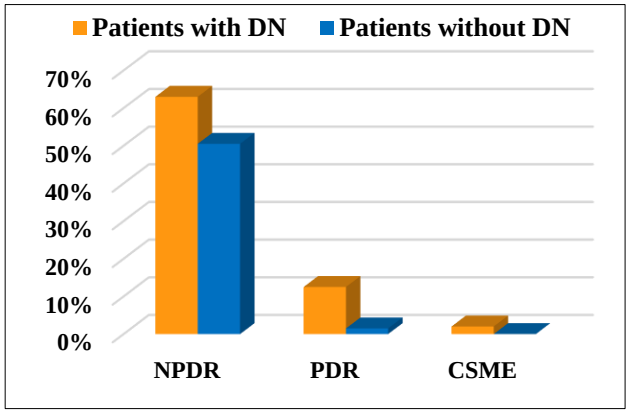

Figure 4: Percentage of different types of diabetic retinopathy in patients with and without nephropathy.

The distribution of various types of retinopathy was 63% NPDR, 12.5% PDR and 2% CSME in patients of DN and 50.5% NPDR, 1.5% PDR, and none with CSME, in patients without DN (Figure 4).

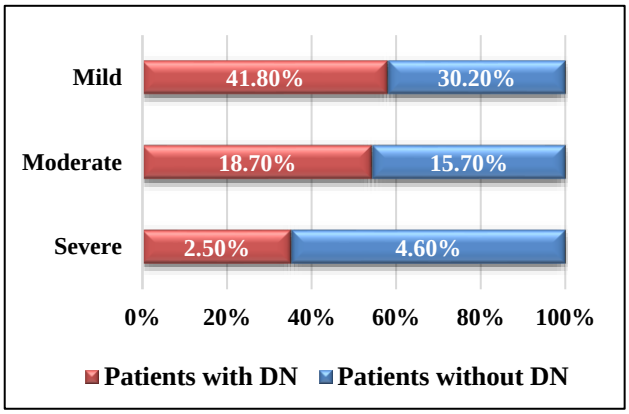

Figure 5: Severity of Non-Proliferative Diabetic Retinopathy (NPDR) in patients with and without nephropathy.

The NPDR was further categorized as mild, moderate or severe among all the patients who had DR. In patients with DN, who had NPDR, 41.8% had mild NPDR, 18.7% had moderate NPDR while 2.5% had severe NPDR. In patients without DN, 30.2% had mild NPDR, 15.7% had moderate NPDR while 4.6% had severe NPDR (Figure 5).

Table 2: Distribution of diabetic retinopathy in patients without and with Diabetic Nephropathy (DN).

Fundoscopic evaluation	Patients without DN (n=200)	Patients with DN (n=200)	p value
Normal	96(48%)	45(22.5%)	
Retinopathy	104(52%)	155(77.5%)	
I. NPDR	101(50.5%)	126(63%)	
II. PDR	3(1.5%)	25(12.5%)	
III. CSME	0	4(2%)	<0.001
Values are depicted as n (%), p-values calculated by chi-square test; p < 0.001 is considered to be statistically significant			

DISCUSSION

The results of this study indicate that all types of DR are more common in patients with DN. It was also noted that older age, longer duration of DM and worse glycemic control were associated with greater frequency of DR. The high association between DN and DR complications (both microvascular) in type 2 DM is due to similar pathogenesis of both these microvascular complications.

The findings in this study are in agreement with previous studies that have shown that diabetic retinopathy is more

common in patients with nephropathy.[1-3] However, there were some key differences between demographics compared to the previously reported results. The mean duration of diabetes among this study group was shorter compared to earlier reports, thereby suggesting faster onset of development of DR in patients.[2,5]

It was also observed in this study that subjects with nephropathy had worse glycemic control compared to those without DN. Glycemic control and eGFR both were found to have a strong association with DN which was statistically significant ($p<0.001$). This has been seen in earlier studies as well and re-emphasizes the importance of optimum glycemic control for preventing microvascular complications.[9,10]

This study showed that common co-morbidities associated with DN were CAD, hypertension, dyslipidemia and obesity. This finding is similar to that seen in other studies.[10,11] However, out of these, only CAD, hypertension and dyslipidemia had an association which was statistically significant (Table 1). Although obesity was more frequent in those without DN, it was not statistically significant.

It was seen in this study, that 77.5% patients of DN had DR which was significantly higher than in patients without DN (52%) (Figure 2 and 3). This may be due to a greater age and worse glycemic control in group of patients. Similar findings are seen in other studies also.[12,13] Many population-based studies have shown associations of glycosylated hemoglobin, blood pressure, and serum total cholesterol with the incidence and progression of retinopathy and other micro- and macrovascular complications.[13,14]

The distribution of various types of retinopathy in this study was 63% NPDR, 12.5% PDR and 2% CSME in patients of DN and 50.5% NPDR, 1.5% PDR, and no CSME, in patients without DN (Figure 4). Other studies also showed similar findings. Rani et al, in their study suggested that the association between microalbuminuria and DR could be explained by the fact that microalbuminuria might represent a state of generalized vascular dysfunction.[15-17] In this study, it was seen that amongst patients with DN, Non-Proliferative Diabetic Retinopathy (NPDR) was the most common form of retinopathy seen (63%). In these, 41.8% had mild NPDR, 18.7% had moderate NPDR while 2.5% had severe NPDR (Figure 5). On comparing the severity of NPDR, in patients with and without DN, it was observed that, in patients without DN, more cases of severe NPDR were seen. (4.6% versus 2.5% respectively) (Figure 5). This result is inconsistent with some previous studies that have shown the presence of severe NPDR to be more in cases with the individuals with DN. This finding may be partially explained by the smaller sample size. Besides, it is possible that genetic polymorphism of candidate genes may be responsible to be the main reason for this variation in susceptibility.[18] Identification of genetic determinants of DR will improve understanding of the development and progression of this severe disorder.[19]

Retinopathy has also been thought to develop due to systemic microvascular damage secondary to diabetes, which leads to breakdown of the retinal tissue- blood vessel barrier.[20] Patients with DN may also be inherently at increased risk for DR or other types of serious ophthalmic lesions caused by similar microvascular damage. Besides, there are several genes reportedly associated with susceptibility to DR and DN both.[19,21] The specific mechanisms leading to the occurrence of DR and DN have not been defined so far. These findings suggest that authors could identify the individuals who need aggressive treatment with drugs so that microvascular complications can be minimized.

Even with the availability of better treatment targets and therapeutic options, the association between DN and DR still remains the same. Studies have speculated that similar pathogenesis or molecular pathways lead to the development of diabetic renal and retinal microvascular injury.[4,22] They have suggested that the higher association rates of DN and DR may be because the patients who have already developed DR are more vulnerable to develop DN. It has also been suggested that the pre-existence of one microvascular complication (DR or DN) may contribute to the development of another one. Hence, if either of the micro-vascular complication is noticed, the co-existence or progression to others should be sought for. This study had few limitations. Firstly, it was a study at a single centre which may have led to a small sample size and also sampling bias. Secondly, the causality between progression of DN and DR could not be proved. Thirdly, authors did not evaluate the therapeutic interventions which may have had potential impact on renal disease prognosis. Even though, significant association of DR was found, more prospective studies are needed to know the exact mechanism of how these diabetic microvascular diseases correlate. The strengths of this study are that it was done in a real-life practice setting and focusing on the association between two important microvascular complications which have a major contribution to diabetic morbidity. This will help in early detection of both these dreaded complications. Despite this study being carried out in a single hospital setting, the fact that the patient population comprised of defence personnel and their families coming from various parts of the country, they represented varied populations. This study can be further carried out in various parts of the country with a larger sample size. Other complications of type 2 DM may be taken into account for subsequent studies and adequately followed up.

ACKNOWLEDGEMENTS

Author express their sincere thanks to the Department of Ophthalmology, AFMC Pune for all the support in making this study successful.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee AFMC Pune, India

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Cite this article as: Mohan C, Muthukrishnan J, Mishra S, Nair BT. Association of diabetic nephropathy with diabetic retinopathy in type 2 diabetes mellitus patients. Int J Adv Med 2020;7:17-21.