Visual Morbidity in Diabetic Retinopathy Associated with Diabetic Nephropathy - Our Experience in a Multispecialty Tertiary Hospital in Chennai, India

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ABSTRACT

BACKGROUND

The increased prevalence of diabetes mellitus (DM) worldwide has resulted in worsening diabetic retinopathy (DR) and nephropathy. The pathophysiological changes that occur at a cellular and anatomical level are similar in DR and DN. The risk factors for DR and DN are common hence investigating both is paramount to reduce morbidity. We wanted to study the association of diabetic retinopathy and diabetic nephropathy, their ophthalmic features, patterns of vision loss and extent of ocular morbidity.

METHODS

This is a retrospective observational study performed on 100 diabetic patients over 2 years. Patients with a confirmed diagnosis of DN based on clinical evaluation and laboratory tests were included. Ophthalmic evaluation and investigations were done and DR was classified based on early treatment diabetic retinopathy study (ETDRS).

RESULTS

Mild non-proliferative diabetic retinopathy (NPDR) occurred in 60 %, moderate to severe NPDR in 9 %, proliferative diabetic retinopathy (PDR) in 4 % and no diabetic retinopathy in 27 %. Macula was involved in 48 % with clinically significant macular edema (CSME) in 33 % and ischemic maculopathy in 5 %. Retinopathy occurred in 3 % after 5 years and in 40 % after 20 years of DM. The incidence of DN +DR was 65 % and statistical significance was noted with longer duration of diabetes, higher serum creatinine, proteinuria, lower haemoglobin, decreased GFR, higher age and higher lipid levels (P = 0.04). Improvement in vision was seen in 63 % after blood sugar control with laser photocoagulation, 27 % with laser alone and 7 % of patients with intravitreal anti-VEGF

CONCLUSIONS

DR and DN have an overlapping significant association and all patients have to be screened for both to prevent ocular morbidity.

KEY WORDS

Diabetic Retinopathy, Diabetic Nephropathy, Vision, Glomerular Filtration Rate, Macular Edema.

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BACKGROUND

The increased prevalence of diabetes mellitus (DM) worldwide has resulted in worsening diabetic retinopathy (DR) and nephropathy.[1] The similarity of features in diabetic retinopathy and nephropathy is due to the resemblance of microvasculature.[2] The duration of diabetes, glycaemic control, elevated blood pressure, lipid profiles, serum HbA1c, change in retinal vessel calibre and genetic factors contribute to the progression of DR.[3] Diabetic nephropathy (DN), is an important precursor to the development of chronic kidney disease.[4] DN is characterized by a reduction of glomerular filtration rate (GFR) and albuminuria.[5] The presence of albuminuria signifies the presence of vasculopathy and endothelial abnormalities that worsen morbidity.[6]

As in the case of DR, the major risk factors identified for DN include prolonged duration of diabetes, poor glycaemic control, and hypertension. Patients with severe diabetic nephropathy sometimes present with proliferative retinopathy, persistent macular oedema or / and haemorrhagic complications including neovascularization and vitreous haemorrhage.[7] Optimizing blood-sugar together with tight control of blood pressure can reduce the risk of developing both DR and DN. These were evaluated in the prospective diabetes study done in the United Kingdom prospective diabetes study (UKPDS) trial.[8]

Chronic hyperglycaemia leads to basement membrane thickening causing loss of pericytes, endothelial cell proliferation and an alteration in blood-retinal barrier. Aggregation of platelets and vascular occlusion lead to hypoxia of the retina and advancement of diabetic retinopathy changes. The disarrangement of microstructure and dysfunction of microcirculation lead to vascular hyperpermeability and microaneurysm formation. Excessive vascular leakage with resultant loss of proteins and lipids from the vessel wall leads to the accumulation of fluid in the inner layers of the retina resulting in diabetic macular oedema.[9]

The newer inflammatory theory which puts vascular endothelial growth factors (VEGF) in the centre of the aetiology of diabetic macular oedema and retinopathy says that the accumulation of advanced glycated end–products (AGEs) leads to the inflammation and release of mediators such as intracellular adhesion molecules (ICAM) and vascular cell adhesion protein (V - CAM) which in turn increase vascular permeability and cause progression of retinopathy and macular oedema.[10]

The purpose was to study the association of diabetic retinopathy and diabetic nephropathy, their ophthalmic features, patterns of vision loss and extent of ocular morbidity.

METHODS

This is a retrospective observational study from Sri Ramachandra Institute of Higher Education and Research, Chennai, that was performed on 100 patients for 2 years from June 2018 to April 2020 at a tertiary care eye centre in India. An ethics committee approval was obtained (CSP - MED / 21 / MAR / 67 / 47). All patients with a confirmed diagnosis of DN based on the American diabetes association guidelines for micro and macroalbuminuria[11] were included in the study, the features of which are depicted in table 1. Clinical evaluation and laboratory tests such as blood sugars, HbA1c, fasting lipid profile, complete blood count, renal function test, urine analysis to look for protein (specifically albumin and globulin), red blood cells, specific gravity and signs of previous infections were noted. We also measured serum uric acid, blood urea nitrogen, serum creatinine and serum electrolytes (potassium, sodium and magnesium). Glomerular filtration rate was calculated for all patients with DN using bodyweight and their creatinine values, according to Cock Croft Equation.[12]

GFR = 140–AGE in yrs. × WEIGHT in kg / 72 × CREATININE in mg / dl. Patients with advanced kidney disease were subjected to a renal biopsy to look for microvascular complications and study the histopathological changes related to diabetes.

All type1 and type 2 diabetes mellitus patients inclusive of both new and old were incorporated in the study. Patients with pre-existing comorbidities were excluded from the study. A detailed history was obtained with regard to treatment, the drugs used with dosage and duration.

Ophthalmic evaluation consisted of slit-lamp examination, indirect ophthalmoscopy, tonometry, and refraction. Ancillary ophthalmic investigations including colour vision, Amsler's grid, perimetry, fundus fluorescein angiography, optical coherence tomography and B scan ultrasonography were performed during the initial and follow up visits.

Patients were reviewed every month to look for a response to treatment and to detect all ocular complications. All patients had a follow up of at least one year. During active disease, weekly reviews were done. As part of monitoring, complete blood counts, renal function tests and blood sugars were done every 3 months. Retinopathy changes were classified into non-proliferative and proliferative diabetic retinopathy. The non-proliferative variant was divided into mild, moderate and severe using ETDRS classification and the presence of clinically significant macular oedema was noted.[13]

Stages	Albuminuria Cut-Off Values (Ref. 14)	Clinical Characteristics (Ref. No.)
Micro-albuminuria	20 – 199 µg/min	Abnormal nocturnal decrease of blood pressure and increased blood pressure levels (163)
	30 – 299 mg/24h	Increased triglycerides, total and LDL cholesterol, and saturated fatty acids (164, 165)
	30 – 299 mg/g*	Increased frequency of metabolic syndrome components (166)
		Endothelial dysfunction (167)
		Association with diabetic retinopathy, amputation, and cardiovascular disease (168)
		Increased cardiovascular mortality (2, 169)
		Stable GFR (82)
Macroalbuminuria†	≥ 200 µg / min	Hypertension (99)
	≥ 300 mg / 24h	Increased triglycerides and total and LDL cholesterol (170)
	≥ 300 mg / g	Asymptomatic myocardial ischemia (171, 172)
		Progressive GFR decline (83, 84)

Table 1. Diabetic Nephropathy Stages: Cut-Off Values of Urine Albumin for Diagnosis and Main Clinical Characteristics

Statistical Analysis

Sample size calculation: Sample size was calculated keeping a study done by Samreen Jamal et al. to analyse the "Frequency and grading of diabetic retinopathy in diabetic end-stage renal disease patients".[14] Keeping an alpha error of 5 % and a CI of

95 %, the sample size was calculated as 96 which we rounded off to 100.

Analysis - All collected data were analysed using IBM SPSS statistics software, version 23.0. The frequency analysis for distribution of data and percentage analysis was done for categorical variables. Mean and standard deviation was analysed using continuous variables. Kappa coefficient was used for correlating test values. Statistical significance of categorical data was done using chi-square test and a probability value of $P < 0.05$ was considered as statistically significant.

RESULTS

This was a retrospective study performed on 100 patients. We had 16 % patients with type 1 and 84 % with type 2 DM. No features of diabetic retinopathy were seen in 27 %, mild non-proliferative diabetic retinopathy in 60 %, moderate to severe non-proliferative diabetic retinopathy (NPDR) in 9 %, and proliferative diabetic retinopathy (PDR) in 4 % of the cohort. This group was further divided into those with isolated DR group which accounted for 35 % and the DR with DN in association accounted for 65 %.

In the set with combined retinopathy and nephropathy, mild NPDR occurred in 29 %, moderate NPDR in 15 %, severe NPDR in 9 %, very severe NPDR in 5 % and PDR in 7 %. There was a definite increase in the prevalence of retinopathy in those with nephropathy. Involvement of the macula was present in 48 % of patients.

Clinically significant macular oedema was noted in 33 % and ischemic maculopathy in 5 %. Retinopathy was related to the presence of associated blood pressure, serum creatinine, and glomerular filtration rate and serum potassium levels. The prevalence and severity of retinopathy were associated with a longer duration of diabetes. Incidence of retinopathy with regard to duration occurred in 3 % after 5 years of DM and in 40 % after 20 years.

Among these 100 patients, 60 were males and 40 were females. A renal biopsy had been performed in 21 patients and the findings were predominantly interstitial inflammation with cellular infiltration in 15 of those patients. The mean GFR was 57 ± 33 mL / min / 1.73 m^2, and proteinuria level was 4.21 g / day (range, 0.03–24.00 g / day).

The isolated DR group accounted for 35 % and the DR with DN accounted for 65 %. Compared with the DN group, patients in DN + DR group were more likely to have a longer duration of DM, higher levels of serum creatinine and proteinuria, lower levels of haemoglobin, increased incidence of haematuria, and decreased GFR than participants without DR. This was found to be statistically significant with P = 0 .04. There was a considerable effect of age, incidence of hypertension, blood urea nitrogen (BUN), obesity, blood sugar levels (FBS, PPBS and HbA1c), uric acid, lipid profile (high-density lipoprotein, low-density lipoprotein, triglyceride, total cholesterol in those who developed DR in DN. Another significant risk factor that was identified in association with DR was haematuria which was seen in 12 % of patients. 21 % of patients with renal failure had no evidence of retinopathy.

An improvement in vision was noted in 63 % following control of blood sugar combined with laser photocoagulation, 27 % with laser photocoagulation alone and in 7 % of patients with intravitreal anti-vascular endothelial growth factor.

Severity of Retinopathy	Number of Participants (N)	Percentage %
Mild	44	60
Venous dilatation	26	36
Microaneurysms	20	27
Hard exudates	15	21
Moderate to severe	7	9
Cotton wool spots	7	9
IRMA	5	6
Proliferative diabetic retinopathy	3	4
NVD	1	1
NVE	2	3

Table 2. No. of Participants in Which Various Clinical Signs of Retinopathy Were Seen in Our Study Population

Classification of Patients	Number of Participants (N)	Percentage %
Retinopathy only	26	35
Nephropathy with retinopathy	47	65

Table 3. No. of Participants with Retinopathy and Nephropathy

Grade of Retinopathy	No of Participants (N)	Percentage
Mild NPDR	14	29 %
Moderate NPDR	7	15 %
Severe NPDR	4	9 %
Very Severe NPDR	2	5 %
PDR	3	7 %

Table 4. Association of Diabetic Retinopathy with Nephropathy

N = All patients with diabetic retinopathy and nephropathy

DISCUSSION

DM affects about 463 million people worldwide. Diabetes currently affects more than 62 million Indians, which is more than 7.2 % of the adult population.[15] A single pathway due to microvascular damage appears to be the cause of renal and retinal involvement in DM. This link between both organs getting involved as a consequence of microvascular disease can have varying consequences on vision and renal function both of which can affect the quality of life. They coexist or may occur in isolation and need evaluation to be performed to prevent life-threatening complications.

Patients with diabetes mellitus and diabetic retinopathy (DR) are prone to develop diabetic nephropathy (DN) and the incidence of retinopathy is higher in those with DN. In this study, we aimed to clarify the relationship between DR and the progression of DN in these patients. Our findings indicated that the severity of glomerular lesions was significantly associated with DR[16] and DR and was an independent risk factor for the renal outcomes in patients with DN. An exact incidence on which precedes the other is difficult to deduce as it varies based on other systemic influences. However, a definite correlation of severity and progression suggesting that DR may predict the renal prognosis of patients in DN and vice versa was established on our study patients.

An estimation of the presence and severity of retinopathy is usually made based on direct ophthalmic evaluation of anatomical changes combined with an evaluation of visual acuity with supportive evidence from fundus fluorescein angiography [FFA] and optical coherence tomography [OCT]. Nephropathy unlike retinopathy is defined using functional abnormalities such as GFR, proteinuria, haematuria and microalbuminuria.

Sabanayagam et al. demonstrated that CKD is usually associated with diabetic retinopathy only when albuminuria is

present and this demonstrates the need for albuminuria to be an associated feature of CKD.[17]

Kimmelstiel and Wilson in 1936 described a clinicopathological syndrome characterized by hypertension, renal failure with albuminuria, widespread oedema and retinitis in longstanding and often mild diabetics whose kidneys demonstrated histologically what they termed intercapillary glomerulosclerosis.[18] This disease is extensively associated with nephrotic syndrome and long-standing diabetes.

This requires a renal biopsy for confirmation. Many of our patients underwent renal biopsy to look for interstitial changes in the kidney that could have probably led to the microvascular changes that have occurred at the cellular level. Many patients with ischemic nephropathy and Kimmelstiel Wilson disease commonly present with cotton wool spots and arteriolar narrowing with retinal exudates which was a consistent retinal feature in many of the patients in our study. It is however essential to distinguish this from ischemic nephropathy and hypertensive retinopathy. The role of free fatty acids (FFA) to assess the ischemic changes in DR becomes essential and capillary dropouts and foveal avascular zone (FAZ) expansion are the key findings in ischemic retinopathy. A strong suspicion of nephropathy must be made in all patients presenting with retinopathy as suggested by Lee et al.[19] demonstrated that ischemic DR characterized with extensive capillary nonperfusion is a possible prognostic factor for the progression of CKD and a strong index of suspicion must be maintained in patients who present with profound visual loss that is out of proportion with retinal findings which is strongly suggestive of ischemic maculopathy.

However, this relationship between anatomical changes causing retinopathy and functional changes in nephropathy in DM has remained inconclusive. Studies have also reported the incidence of both features in isolation. Advanced renal changes have occurred in the absence of retinopathy.[20]

We found that there was a significant increase in the incidence and progression of retinopathy in patients with DN. The severity of retinopathy increased with the increasing severity of nephropathy. Diabetic maculopathy also correlates with DN. Biswas et al. studied diabetic maculopathy and diabetic nephropathy in 100 patients in the Indian population and found a strong association between the two.[21]

The greatest association was found between DM, hypertension and increased lipid profile (triglycerides, LDL, cholesterol) with all three playing a role in the severity of retinopathy and nephropathy.[22] In a study by JL Wilkinson et al. they established these risk factors and found a strong correlation between vision loss, CKD and these risk factors with increasing prevalence of PDR in patients with advanced CKD.[23] Our results are also similar to a study done by Ahmed M et al. in the Sudanese population and these results show us that hypertension and hyperlipidaemia are important risk factors for nephropathy and retinopathy across population demographics.[24] Among laboratory tests for DM, HbA1c seemed to have a bigger role in the determination and assessment of the visual status. Clinically significant macular oedema [CSME] was associated with higher LDL, total cholesterol values, HbA1c levels and raised serum creatinine. The decreased prevalence of macular oedema is probably related to modifications of osmotic pressures that occur during dialysis.[25]

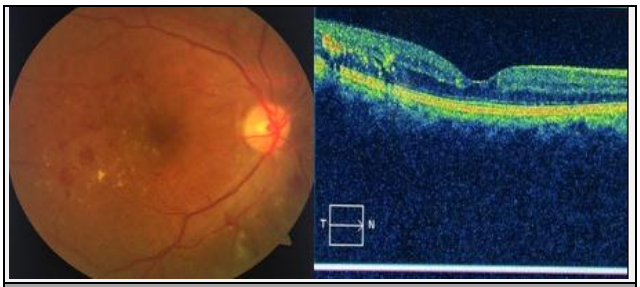

Figure 1. Mild NPDR with CSME with Corresponding OCT Image Showing Diffuse Macular Oedema with Increased Macular Thickness

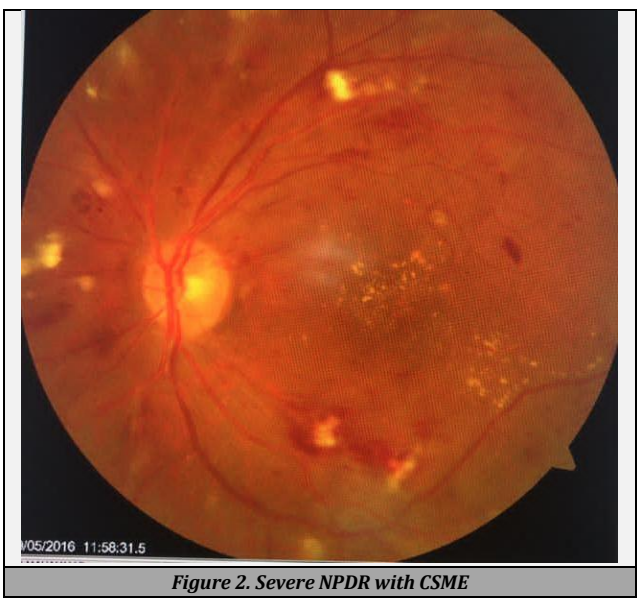

Figure 2. Severe NPDR with CSME

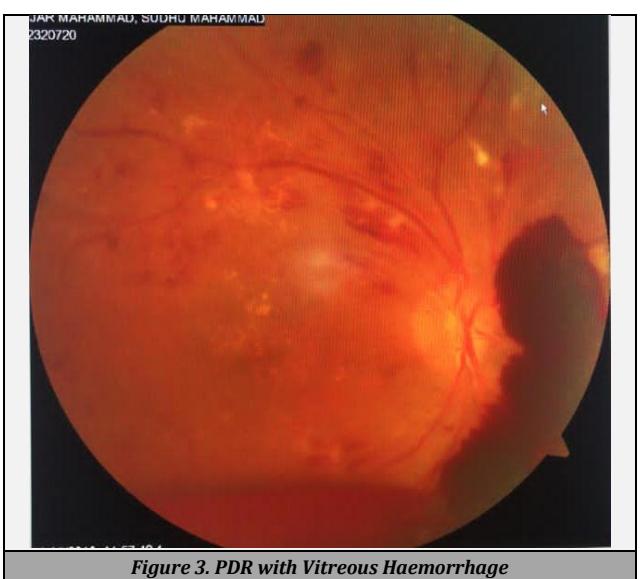

Figure 3. PDR with Vitreous Haemorrhage and Sub Hyaloid Haemorrhage

Microalbuminuria correlates well with diabetic retinopathy especially proliferative retinopathy. In a population-based study by Sobngwi et al. in Cameroon they found microalbuminuria to be significantly elevated in patients with advanced retinopathy.[26] Won Jee lee et al. looked at the relationship between diabetic nephropathy and retinopathy in the Korean population and found that the severity of nephropathy correlated with the severity of retinopathy,[27] The likelihood of manifesting nephropathy was higher in PDR patients. These findings correlated with the

findings in our study. Many patients who presented with vitreous haemorrhage or advanced PDR had poorer visual outcomes and had lower baseline GFR rates and more advanced kidney damage. The visual recovery in these patients was poor and the end-organ damage was advanced. Significant visual and systemic morbidities were associated with advanced kidney damage. In a study by Manaivat et al. they divided the population based on mild-moderate and severe retinopathy and correlated the microalbuminuria levels in these three levels and found that the levels were elevated with the progressive increase in severity of diabetic nephropathy.[28] The results were similar to ours and the conclusions were extrapolatable. At the end of the study, we were able to identify two sets of patients. The first set had only diabetic retinopathy, and the second, with diabetic retinopathy and DN with renal lesions (microalbuminuria).

In the first set, the duration of diabetes mellitus and HbA1c were the most important risk factors and in the second set, HbA1c levels, renal profile and blood pressure were the most important. The progression of DR with vision-threatening complications and coexisting DN depended on the initial findings on presentation, duration and control of diabetes and was compounded by comorbidities including hypertension, dyslipidaemia, and serum creatinine levels.

CONCLUSIONS

DR and DN remain an enigmatic topic as there can be overlapping features and variable courses with relevance to both. We found that significant association does exist and that all patients with retinopathy have to be screened for nephropathy and vice versa. This methodical protocol in all patients with DM will prevent vision-threatening complications and life-threatening consequences.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.
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