ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 05 | May - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CLINICAL CORRELATION OF DIABETIC RETINOPATHY WITH NEPHROPATHY

Ophthalmology

Dr. Harsha Pawar* M S Ophthalmology*Corresponding Author
Dr. Sonia Nankani M S Ophthalmology
Dr.Vijay Daberao

KEYWORDS

INTRODUCTION

Diabetes mellitus (DM) is a chronic disorder characterized by persistent hyperglycemia. Epidemiological data in India shows an upward trend in the prevalence, with 32 million people suffering from DM in the year 2000 to 79 million in the year 2010 thus making India the 'Diabetic Capital of the World.' [1,2] DM is classified on the basis of pathogenic process into two broad categories- Type 1 and type 2 DM. Autoimmunity against insulin-producing beta cells causes type 1 DM results in total or near-total insulin insufficiency, while type 2 DM is a diverse collection of diseases marked by varying degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production. Over time, if poorly controlled, DM can affect multiple organ systems and is responsible for the morbidity and mortality associated with the disease. Diabetes related complications affect generalized macrovasculature and microvasculature of various vital systems leading to retinopathy, nephropathy and neuropathy.

Diabetic Nephropathy (DN)

DN is a syndrome comprising of persistent proteinuria, hypertension, and low glomerular filtration rate (GFR) leading to chronic loss of kidney function. In India, about 15-35% of patients with end-stage renal disease (ESRD) have underlying diabetic nephropathy. [3,4] Nephropathy affects 25-45% of type 1 diabetics and approximately 50% of type 2 diabetics at some point in their lives; the most common time for nephropathy to develop being 10–15 years from the commencement of DM. [5] Some of the risk factors for development of diabetic nephropathy are duration of diabetes, glycemic control, male sex, familial clustering, hypertension, hyperlipidemia, and smoking. The risk of developing nephropathy increases as the duration of diabetes increases, with a cumulative risk of 50% after 20 years. [6] Clinical diabetic nephropathy is primarily a consequence of extracellular matrix accumulation due to imbalance between its production and rate of removal, leading to glomerulosclerosis. There is also a component of mesangial expansion and reduced podocyte number. [7,8] All these changes lead to restriction of filtration surface and leakage of albumin and disease progression.

Diabetic retinopathy (DR)

DR is a microvascular consequence of diabetes that is a leading cause of legal blindness across the world. According to World Health Organization (WHO), DR is responsible for 3–7% of total blindness in Asia. [9] And in India, the prevalence of DR in general population is about 3.5%. [10] Blindness in patients with diabetic retinopathy is a consequence of the occurrence of diabetic maculopathy caused by retinal hypoxia and increased vascular permeability or proliferative diabetic retinopathy. Extensive retinal hypoxia due to closure of a large part of capillary network causes neovascularization, which is a hallmark of proliferative diabetic retinopathy, in which fragile new vessels grow from post capillary venules. Risk factors for development of diabetic retinopathy includes duration of diabetes, glycemic control, age, hypertension, renal disease, dyslipidemia, pregnancy, ocular factors like presence of posterior vitreous detachment and previous cataract surgery. [11,12] Out of these, duration of diabetes and degree of glycemic control are the strongest predictors of the development of retinopathy. [13]

Purpose

The exact pathogenesis of frequent occurrence of retinopathy in patients with diabetic nephropathy is not known. However, both retinopathy and nephropathy are microvascular in origin and have similar risk factors such as association with long-standing diabetes, [14] being general public health problems, it was worthwhile to investigate the link between the two. Understanding the association between different complications of diabetes could lead to a better understanding of the disease processes and subsequently better screening and management techniques. The aim of this study was to evaluate for the presence of retinopathy in patients with diabetic nephropathy and also to determine the frequency of association of severity of nephropathy with that of retinopathy.

MATERIAL AND METHODS

This prospective observational study was conducted in the Nephrology and Ophthalmology outpatient and inpatient departments of Bombay Hospital. Permission from institutional ethics committee was taken prior to commencement of study and prior written informed consent was taken from every patient before inclusion in study. Thirty adult patients aged >18 years of either sex were recruited between December 2012 to September 2014.

INCLUSION CRITERIA:

Patients with diabetic nephropathy (due to underlying type 1 or 2 DM of any duration) giving written informed consent for participation were enrolled in the study.

EXCLUSION CRITERIA:

Patients with uncontrolled hypertension, congestive cardiac failure and active urinary tract infection, other ocular conditions like glaucoma, myopia, degenerative or dystrophic conditions of the retina, and any history of ocular surgeries, ocular inflammations and ocular trauma in the past were excluded from the study.

Measurements and variables:

A] For nephropathy: All patients were evaluated by the nephrologists based on Urine albumin creatinine ratio (U.ACR) value staging of chronic kidney diseases (CKD). Urine samples were collected and protein values obtained using automated urine protein analyzer using turbidimetric method. Diabetic nephropathy was categorized based on presence of microalbuminuria (30-300 mg/ 24 hr. urine protein), macroproteinuria (>300 mg/ 24 hr. urine protein) and massive proteinuria/ESRD (>3000 mg/ 24 hr. urine protein).

B] Ophthalmic evaluation for retinopathy: Patients recruited in the study also underwent detailed ocular examination including best-corrected visual acuity (BCVA) using Snellen charts, color vision, Amsler grid, anterior segment slit lamp biomicroscopy, applanation tonometry, and fundus evaluation using direct/ indirect ophthalmo scopy. Those showing diabetic retinopathy were graded according to Early Treatment Diabetic Retinopathy Study (ETDRS) classification into mild, moderate, severe and very severe non-proliferative diabetic retinopathy and Proliferative diabetic retinopathy. And diabetic macular edema was categorized into CSME (Clinically significant macular edema) and non-CSME.

STATISTICAL ANALYSIS:

Numerical data is expressed as frequency and percentages and categorical data analyzed using Chi-square test. Statistical analyses were performed using SPSS software (Version 22). P-value of less than 0.05 was considered to be statistically significant.

RESULTS

Thirty patients were included in the study out of which 22 (73%) were males and 8 (27%) were females. The mean age was 57.13 years and

majority (73%) were distributed in the age group of 50-69 years. The duration of diabetes amongst the patients ranged from 5 to 25 years and 17 (57%) patients had diabetes of >10 years duration. 13 (43%) patients were hypertensive. Out of 30 patients, 3 (10%) were on insulin and 27 (90%) were on oral hypoglycemic agents.

Table 1 shows distribution of study population according to severity of DN. Out of 30 patients, majority (56.67%) had macroproteinuria and also a significant proportion i.e. (23.34%) had microalbuminuria, while 20% of the patients had massive proteinuria.

Table 1: Distribution of study population according to the severity of nephropathy

Severity of diabetic nephropathy	Frequency	Percentage
Microalbuminuria	7	23.34%
Macroproteinuria	17	56.67%
Massive proteinuria	6	20%
Total	30	100%

Table 2 shows distribution of severity of nephropathy according to the grade of retinopathy. N=24 i.e. 80% of the patients of diabetic nephropathy exhibited some degree of retinopathy. Amongst the 7 patients with microalbuminuria, 4 patients did not have any retinopathy while in macroproteinuria group (n=17) a significant proportion of patients i.e., 65 % (n=11) had mild to moderate NPDR. Amongst the 6 patients with massive proteinuria, 50% patients (n=3) had PDR. PDR was also seen in 1 patient with macroproteinuria. The relationship between proteinuria and retinopathy was found to be statistically significant (p=0.0003).

Table 2: Distribution of severity of nephropathy according to staging/grade of retinopathy

Nephropathy Staging	Grade of Retinopathy				
	No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
Microalbuminuria	4	2	1	0	0
Macroproteinuria	2	8	3	3	1
Massive proteinuria	0	0	1	2	3
Total	6	10	5	5	4
Chi-square value = 21.19, p-value = 0.0003**					

DR = Diabetic retinopathy, NPDR = non-proliferative diabetic retinopathy, PDR = Proliferative diabetic retinopathy Most common symptom experienced by the patients with retinopathy was blurring of vision (52%) and most common range of duration of symptom was found to be 6 to 12 months. Figure 1 depicts relationship between severity of nephropathy and retinopathy. 4 patients with microalbumi nuria had no retinopathy, while in patients who had mild or moderate NPDR, microalbuminuria was present in 2 and 1 patient respectively. N=8 patients who had macroproteinuria also had mild NPDR. In severe NPDR, none had microalbuminuria, 3 patients had macroproteinuria while 2 patients had massive proteinuria. PDR was observed in a single patient with macroproteinuria and 3 patients who had massive proteinuria.

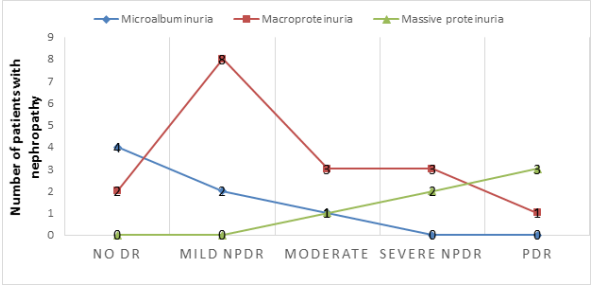

Figure 1: Trend between severity of nephropathy and retinopathy

DR = Diabetic retinopathy, NPDR = non-proliferative diabetic retinopathy, PDR = Proliferative diabetic retinopathy

In our study, n=12 (40%) patients exhibited maculopathy and out of them 7 (58%) had clinically significant macular edema (CSME). Most of the CSME patients i.e., 5 out of 12 (71.42%) patients were from macroproteinuria group. The distribution of severity of nephropathy according to CSME was not statistically significant (p=0.42). Table No. 3 shows distribution of severity of DN according to CSME.

Table 3: Distribution of severity of nephropathy according to CSME status

Nephropathy Staging	Maculopathy Status		Total
	CSME	Without CSME	
Microalbuminuria	0	0	0
Macroproteinuria	5	5	10
Massive proteinuria	2	0	2
Total	7	5	12
Chi-square value = 1.71 p-value = 0.42			

CSME=Clinically significant macular edema

Out of 30 patients, n=24 (80%) had uncontrolled diabetes i.e., HbA1c >7 out of which 22 patients exhibited retinopathy as shown in Table 4. Table 5 shows the relationship between duration of diabetes and severity of retinopathy, which was not statistically significant. Although there was a trend that the longer the DM, the more serious the retinopathies. Amongst patients whose DM duration ranged from 5-10 years (n=13), mild and moderate NPDR was seen in 9 patients, while severe NPDR was seen in a single patient and PDR was seen in none. In patients whose DM duration was >10 years, n=2 patients had moderate NPDR, while the 3 categories- mild and severe NPDR and PDR had 4 patients each.

Table 4: Distribution of severity of diabetic retinopathy and control of diabetes

Grade of Retinopathy	HbA1c Levels	
	HbA1c <7%	HbA1c ≥7%
No DR	4	2
Mild NPDR	2	8
Moderate NPDR	0	5
Severe NPDR	0	5
PDR	0	4
Total	6	24

Table 5: Distribution of patients according to the duration of diabetes and grades of retinopathy

DM Duration	Grade of retinopathy					Total
	No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	
<5 years	0	0	0	0	0	0
5-10 years	3	6	3	1	0	13
>10 years	3	4	2	4	4	17
Chi-square value 5.97, p-value 0.2014						

DISCUSSION

Diabetes mellitus justifiably known as 'silent killer' as its sequelae diabetic nephropathy remains one of the leading causes of kidney failure [15] and its ocular complication retinopathy is predicted to be the principal reason of new blindness among working population. The World Health Organization (WHO) estimates that diabetic retinopathy is responsible for 3–7% of total blindness in Asia. [16] Out of the many microvascular complications caused by diabetes, nephropathy and retinopathy are unquestionably the major ones. The correlation between diabetic nephropathy and retinopathy is well known in DM type 1 patients. In DM type 2 this correlation is less clear. [17] The present study was conducted to identify the fundus changes pertaining to DR and its correlation with different stages of diabetic nephropathy.

In our study, significant association between albuminuria of varying degrees (indicating diabetic nephropathy) and retinopathy was seen. Parving et al, Lunetta et al. and multiple studies have shown that there is a significant relationship between degree of retinopathy and albuminuria. [18–20] Pavring et al. reported a prevalence rate of 22% for microalbuminuria in diabetes type 2 [18] whereas Lunetta et al. reported a prevalence rate of 15%. [19] The prevalences of microalbuminuria and macroalbuminuria were 25.9% and 14.5% respectively in a study by Manaviat et al. [21] In our study, 23% of patients had microalbuminuria, 57% patients had macroalbuminuria and among them 20% patients had massive proteinuria. This discrepancy was seen because most of our patients had type 2 DM where the time of first presentation could have been late and thirdly the patients were not routinely screened for microalbuminuria. This shows lack of awareness among patients and also general practitioners regarding appropriate screening of patients for microalbuminuria and appropriate referral of these patients to nephrologists and ophthalmologist. Moreover, the severity of renal impairment was found associated with the severity of the damage to the eye in the present study. The proportion of patients with severe

NPDR and PDR was significantly higher than mild to moderate NPDR in the patients having massive proteinuria as compared to patients with microalbuminuria and macroproteinuria. In our study, the prevalence of PDR was 13 % in patients with gross proteinuria and among them 75 % patients had massive proteinuria. In studies done by Phoksunthorn T et al. and Manaviat et al., 201 type 1 and 590 type 2 diabetics were included respectively. Phoksunthorn et al. concluded that microalbuminuria was associated with diabetic retinopathy and is a reliable marker of retinopathy and Manaviat et al. concluded that macroalbuminuria was associated with diabetic retinopathy in type II diabetic patients and is a reliable marker of retinopathy. [21,22]

The prevalence of CSME was 29% in macroproteinuria group and 33% in massive proteinuria group in this study. Manaviat et al. reported a prevalence of PDR to be 17.5% in gross proteinuria patients. [21] Asensio-Sanchez VM et al showed that in patients suffering from severe retinopathies, 37.78 % and 51.11 % exhibited microalb uminuria and macroalbuminuria, respectively and among those patients with macular edema, 31.1% and 40 % exhibited microalbuminuria and macroalbuminuria, respectively. [23] In a cross-sectional study by WESDR those with gross proteinuria were more likely to have signs of any retinopathy, PDR or CSME at baseline evaluation than those without gross proteinuria. Odds of having PDR when gross proteinuria was present was 4.58 for type 1 and 2.71 for type 2 diabetics. For clinically significant macular edema the odds were 2.42 and 1.47 in type 1 and 2 diabetes, respectively. [24]

It is a very well-established fact that duration of diabetes is a strong risk factor for the development and progression of diabetic retinopathy and also the severity of the retinopathy. In patients with type 1 and type 2 diabetes with disease duration of over twenty years, the prevalence of DR is 95% and 60%, respectively. [25] In the current study, we too found positive correlation between duration of diabetes and the severity of diabetic retinopathy however it was not statistically significant. This might be due to small sample size which is one of the major limitations of the study.

Over the years, voluminous information has accumulated on the pathogenesis of diabetes complications like retinopathy. Many clinical trials and researches have yielded fruitful results. These results need to transform into clinical practice amongst ophthalmologist, nephrolo gists and physicians, so as to benefit the patients. Data from many epidemiological studies support nephropathy as a risk indicator and a risk factor and have suggested that these patients benefit from having regular ophthalmic evaluation. Presence of retinopathy is also a risk indicator of sub clinical nephropathy and these patients may benefit from screening for 24 hr urine albumin excretion.

We recommend screening of all diabetic patients for microalbuminuria using 24 hr urine protein evaluation and a baseline fundus examination at the time of diagnosis in type 2 DM. Early detection and treatment of nephropathy could reduce the morbidity and mortality in such patients from other complications of nephropathy.

CONCLUSION

Diabetic retinopathy was more common in patients who had macroproteinuria or severe proteinuria. Also, severity of proteinuria and retinopathy had a statistically significant relationship. On the basis of severity of DN we can predict the presence/absence and severity of retinopathy in diabetic patients. Thus, proteinuria can be employed as a marker of retinopathy.

REFERENCES

1. Noncommunicable Diseases in the South-East Asia Region 2011 Situation and Response.
2. Wild S, Bchir MB, Roglic G, Green A, Sci M, Sicree R, et al. Global Prevalence of Diabetes Estimates for the year 2000 and projections for 2030. 2004 [cited 2022 Mar 7]; Available from: http://diabetesjournals.org/care/article-pdf/27/5/1047/566025/ zdc00 504001047.pdf
3. Andersen AR, Sandahl Christiansen J, Andersen JK, Kreiner S, Deckert T. Diabetic Nephropathy in Type 1 (Insulin-Dependent) Diabetes: An Epidemiological Study. Vol. 25, Diabetologia. 1983.
4. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM. Disparities in Incidence of Diabetic End-Stage Renal Disease According to Race and Type of Diabetes. http://dx.doi.org/101056/NEJM198910193211603 [Internet]. 2010 Jan 14 [cited 2022 Mar 7];321(16):1074–9. Available from: https://www.nejm.org/ doi/10.10 56/NEJM198910193211603
5. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, et al. Prevalence of Complications in IDDM by Sex and Duration Pittsburgh Epidemiology of Diabetes Complications Study II [Internet]. Available from: http://diabetesjournals.org/diabetes/article-pdf/39/9/1116/358138/39-9-1116.pdf
6. Tziomalos K, Athyros VG. Diabetic nephropathy: new risk factors and improvements in diagnosis. Review of Diabetic Studies. 2015;12(1):110–8.
7. White KE, Bilous RW, Marshall SM, Nahas M el, Remuzzi G, Piras G, et al. Podocyte Number in Normotensive Type 1 Diabetic Patients with Albuminuria [Internet]. Available from: http://diabetesjournals.org/diabetes/article-pdf/51/10/3083/ 369644/ db1002003083.pdf
8. Dalla Vestra M, Masiero A, Roiter AM, Saller A, Crepaldi G, Fioretto P. Is Podocyte Injury Relevant in Diabetic Nephropathy? Studies in Patients with Type 2 Diabetes [Internet]. Available from: http://diabetesjournals.org/diabetes/article-pdf/52/4/1031/ 338916/db0403001031.pdf
9. CRSToday | Diabetic Retinopathy in Asia [Internet]. [cited 2022 Mar 7]. Available from: https://crstoday.com/articles/2005-sep/crst1005_16-php-2/
10. Raman R, Rani PK, Reddi Rachepalle S, Gnanamoorthy P, Uthra S, Kumaramanickavel G, et al. Prevalence of Diabetic Retinopathy in India: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study Report 2. Ophthalmology [Internet]. 2009 Feb 1 [cited 2022 Mar 8];116(2):311–8. Available from: http:// www.aaojournal.org/article/S016164200800897X/fulltext
11. Lachin JM. Volume 342 Number 6 Retinopathy and Nephropathy in patients with type 1 Diabetes four years after a trial of intensive therapy. 2000.
12. Klein R, Klein BEK, Moss SE, Davis MD, Demets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: II. Prevalence and Risk of Diabetic Retinopathy When Age at Diagnosis Is Less Than 30 Years. Archives of Ophthalmology [Internet]. 1984 Apr 1 [cited 2022 Mar 8];102(4):520–6. Available from: https://jamanetwork.com/ journals/jamaophthalmology/fullarticle/635006
13. Gupta A, Gupta V, Thapar S, Bhansali A. Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema. American Journal of Ophthalmology [Internet]. 2004 Apr 1 [cited 2022 Mar 8];137(4):675–82. Available from: http://www.ajo.com/article/S0002939403014247/fulltext
14. Macular ischaemia as a marker for nephropathy in diabetic retinopathy: Indian Journal of Ophthalmology [Internet]. [cited 2022 Mar 8]. Available from: https:// journals. lww.com/ijo/ Fulltext/2004/52030/Macular ischaemia_as_a marker for nephropathy in.4.aspx
15. Todkar S. Diabetes Mellitus the ‘Silent Killer' of mankind: An overview on the eve of World Health Day! Journal of Medical and Allied Sciences. 2016;6(1):39.
16. Jay J. Meyer, Changguan Wang, Dhananjay Shukla. Diabetic Retinopathy in Asia. Cataract & Refractive Surgery Today. 2005;
17. Kotlarsky P, Bolotin A, Dorfman K, Knyazer B, Lifshitz T, Levy J. Link between retinopathy and nephropathy caused by complications of diabetes mellitus type 2.
18. Parving HH, Homel E, Mathiesen E. Prevalence of microalbuminuria, arterial hypertension, retinopathy and neuropathy in patients with insulin dependent diabetes. 1988.
19. Lunetta M, Infantone L, Calogero AE, Infantone E. Increased urinary albumin excretion is a marker of risk for retinopathy and coronary heart disease in patients with type 2 diabetes mellitus. Diabetes research and clinical practice [Internet]. 1998 Apr [cited 2022 Mar 13];40(1):45–51. Available from: https://pubmed.ncbi.nlm.nih.gov/9699090/
20. Eggertsen R, Kalm H, Blohmé G. Scandinavian Journal of Primary Health Care The value of screening for retinopathy and microalbuminuria in patients with type 2 diabetes in primary health care. Scandinavian Journal of Primary Health Care [Internet]. 1993;11(2):135–40. Available from: https://www.tandfonline.com/action/ journal Information?journalCode=ipri20
21. Manaviat MR, Afkhami M, Shoja MR. Retinopathy and microalbuminuria in type II diabetic patients. 2004; Available from: http://www.biomedcentral.com/1471-2415/4/9
22. Phoksunthorn T TD. Retinopathy and macro-albuminuria in type 2 diabetic patients. J Med Assoc Thai. 2007;90(4):684–7.
23. Asensio-Sanchez VM, Rodriguez-Delgado B, Herraro GE. Microalbuminuria And Diabetic Retinopathy. Arch Soc Esp Oftalmol. 2008;83(2):85–8.
24. Klein R. Diabetic Retinopathy and Nephropathy. In p. 473–98.
25. Sayin N, Kara N, Pekel G. Ocular complications of diabetes mellitus. 2015; Available from: http://dx.doi.org/10.4239/wjd.v6.i1.92