Study of Clinical Correlation between Diabetic Retinopathy and Diabetic Nephropathy - A Cross-Sectional Observational Study in Eastern India

Bivas Bala[1], Viswanath Pratap[2], Soumi Kanji[3]

[1, 2, 3] Department of Ophthalmology, R.G. Kar Medical College, Kolkata, West Bengal, India.

ABSTRACT

BACKGROUND

In diabetes mellitus microvascular damages at various end-organ frequently occurs and leads to development of diabetic nephropathy as well as diabetic retinopathy. Diabetic nephropathy ultimately causes end stage renal disease. Diabetic retinopathy even at its earlier stage is easily suspected by simple clinical examination in any ophthalmological clinic. We wanted to study the relationship between various stages of diabetic retinopathy with diabetic nephropathy.

METHODS

1209 diagnosed patients of diabetic mellitus were screened for presence of diabetic retinopathy. First comprehensive ophthalmological examination including slit-lamp bimicroscopy and indirect ophthalmoscopy were done and then clinically typing of diabetic retinopathy according to ETDRS classification was done. Then all diagnosed case of diabetic retinopathy further examined for blood Glycosylated haemoglobin, blood urea and serum creatinine to detect diabetic nephropathy.

RESULTS

273 patients were included in this study. Average age of patients was 64.6 years with mean duration of diabetes mellitus was 7.4 years. Patients suffering from severe NPDR and PDR had association with poor control of blood glycosylated haemoglobin. Patients with mild NPDR 31.1 %, Moderate NPDR 52.3 %, severe NPDR 67.4 % and in PDR 65.2 % patient had blood urea more than 40 mg / dl. In mild NPDR group 32.2 %, moderate NPDR 55.4 %, severe NPDR 67.4 % and in PDR group 63.9 % patients had serum creatinine more than 1.5 mg / dl. We have found statistically significant correlation between HbA1c level and severity of diabetic retinopathy. Prevalence of nephropathy increased with increments in the grade of retinopathy.

CONCLUSIONS

A significant number of patients with severe NPDR or PDR had increased blood urea and serum creatinine level. Clinical grading of diabetic retinopathy gives us a clue about the presence of diabetic nephropathy. As diagnosis of diabetic retinopathy is simple and straight forward clinical procedure and it can be done all ophthalmological se up, we recommend all patient with diabetic retinopathy must be screened for nephropathy.

KEYWORDS

Diabetic Retinopathy, Diabetic Nephropathy, Glycosylated Haemoglobin, Blood Urea, Serum Creatinine

Corresponding Author:
Dr. Bivas Bala,
22, 1st by lane, Subhashnagar,
Dumdum Cantonment, Kolkata-700065,
West Bengal, India.
E-mail: bivasbala@gmail.com

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BACKGROUND

Diabetes mellitus, is a very common metabolic disorder due to multiple aetiology in which the hormone insulin is deficient or our body's cells are nonresponsive to insulin itself, characterized by uncontrolled blood glucose level result in microvascular damage of various end organs of human body.[1] As a result, retinopathy, nephropathy, neuropathy and cardiovascular diseases has increased considerably in diabetic population. Of them Diabetic retinopathy and Diabetic nephropathy are two common but serious complications. As they lead to blindness and end stage renal disease, they cause grave impact on patient life as well as our health care system. Now a days diabetes prevalence increases in a rapid rate. According to international diabetes federation more than 550 million people will suffering from diabetes mellitus in 2030. India is also not an exception. Here From 5.5 % in 1990 diabetic prevalence in adult population was 7.7 % in 2016.[2] Diabetic retinopathy is a microangiopathy that shows features of both microvasculature occlusion as well as leakage in the fundus. Due to hyperglycaemia retinal capillaries become weak and there is saccular outpouching which is known as microaneurysm. Sometime these microaneurysm ruptures and causes haemorrhage inside retinal layers as dot-blot or flame shaped haemorrhage. From these fragile capillaries' serous fluid leaks around the macula and causes macular oedema. This macular oedema is the commonest of dimness of vision in diabetic retinopathy. With progression of retinopathy capillaries become occluded and as a consequence there is reduced oxygen supply in retina. As a result, infraction in retinal nerve fiber layer and formation of retinal neo vessel in near future is quite common.

In type 1 diabetes mellitus after 5 years 58 % show evidence diabetic retinopathy. After 15 years 90 % patient must have any form of diabetic retinopathy and 53 % has features of proliferative diabetic retinopathy. In type 2 diabetes prevalence of retinopathy is slightly lower. After 2 years from diagnosis 25 % patients develop diabetic retinopathy but it progresses in a much slower rate. Usually, 20 years after diagnosis only 5 % develop proliferative diabetic retinopathy and 60 % develop in pattern of diabetic retinopathy.[3] In 2009 at Chennai city prevalence of diabetic retinopathy was 18 % among diabetic population.[4] While in 2014 All India Ophthalmological Society Diabetic Retinopathy Eye Screening Study showed a prevalence of 21.7%.[5] Diabetic retinopathy now one of the leading causes of blindness in western world. It increases the chance of loss of vision 25 times higher compared to non-diabetic population. Now also in India blindness due to diabetic retinopathy emerged an important cause of blindness in India. It damages microvascular system of retina in both type I and type II diabetes mellitus. Diabetic nephropathy, a major complication of diabetes ultimately leads to end stage renal disease, In Indian population diabetic nephropathy was the commonest (44 %) cause of ESRD.[6] It is a clinical syndrome associated with persistent albuminuria, decrease glomerular filtration rate with elevated arterial blood pressure. Morphologically, the development of diabetic nephropathy is characterized by progressive thickening of the glomerular basement membrane and by expansion of the mesangial matrix which correlates to glomerular filtration function.[7]

According to Chennai study in 2007 prevalence of overt nephropathy and microalbuminuria was 2.2 and 26.9 %, respectively.[8] Diabetic retinopathy and diabetic nephropathy together contribute a significant percentage morbidity and mortality in diabetic population. They lead to blindness and end stage renal disease, they impose a significant medical, economic, and social costs on the both the patients and health system. Despite the effort the correlation between diabetic retinopathy and nephropathy yet not fully described. One prospective observational study in Denmark concluded that presence of diabetic retinopathy causes a greater rate of decline in renal function.[9] Boelter M.C et al observed in type II diabetes mellitus who has proliferative diabetic retinopathy are more commonly presented with microalbuminuria.[10] In a study conducted by Ali Jawa et al. patient of type 2 diabetes mellitus with proteinuria and nephropathy most likely have also have diabetic nephropathy.[11] Although these data suggested, presence of a pre-existing microvascular complication (retinopathy or nephropathy) may contribute to the development of another, but there is lack of evidence specially from our eastern India.

Therefore, the present study was conducted to study the relationship between glycosylated haemoglobin level and severity of diabetic retinopathy and to know the correlation between diabetic retinopathy and diabetic nephropathy in patients presenting to a tertiary care medical college of eastern India.

METHODS

This was a observational cross-sectional study done at the department of Ophthalmology at R.G. Kar medical college, Kolkata, over a period of 12 months from May 2020 to April 2021 to evaluate the correlation between diabetic retinopathy with diabetic nephropathy. A total of 1209 diagnosed patient of diabetes mellitus attend our out-patient department for screening of diabetic retinopathy during this time. Diagnosis of type 2 diabetes was made according to American Diabetes Association (ADA) criteria

1. A fasting plasma glucose (FPG) level of 126 mg / dL (7.0 mmol / L) or higher, or
2. A 2 - hour plasma glucose level of 200 mg / dL (11.1 mmol / L) or higher during a 75 - g oral glucose tolerance test (OGTT), or
3. A random plasma glucose of 200 mg/dL (11.1 mmol / L) or higher in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, or
4. A haemoglobin A1c (HbA1c) level of 6.5 % (48 mmol / mol) or higher

Inclusion Criteria

1. Patients of diabetes with clinical evidence of diabetic retinopathy.
2. Age more than 18 years.

3. Any gender
4. Patients with or without treatment of diabetic retinopathy.

Exclusion Criteria

1. Pre-existing any retinopathy other than diabetic
2. Nondiabetic renal disorders.
3. Patients unwilling to participate in this study.

After taking written informed consent detailed history regarding his/her diabetes and ocular, renal complain recorded in a pre-structed questionnaires form. Baseline data including age, sex duration of diabetes mellitus, detailed treatment history, past history, family history, drug and personal history were recorded. A comprehensive ophthalmic examination was done meticulously in every patient. First all patient undergo refraction to determine uncorrected visual acuity and best corrected visual acuity. Careful observation of pupillary light reflex observed to rule out any relative afferent pupillary defect. We measure intra-ocular pressure with Goldman applanation tonometry. Then each eye was dilated with a combination of 0.8 % tropicamide and 5 % phenyl epinephrine eye drops (Tropicacyl Plus Eye Drops, Sunways India Pvt Ltd) and fundus examination done by slit lamp bimicroscopy with 90 D lens and by indirect ophthalmoscope with a 28 D lens. Diabetic retinopathy was diagnosed and classified as per International Clinical Disease Severity Scale for Diabetic Retinopathy.

All patients with clinical diagnosis of diabetic retinopathy have undergone blood investigation for Glycosylated haemoglobin, serum urea and creatinine by collecting venous blood sample. According to the level of HbA1c patients were divided into three different groups; very good control group (HbA1c < 6), good control group (HbA1c 6 - 8) and poor control group (HbA1c > 8). Blood urea value more than 40 mg / dl and serum creatinine more than 1.5mg / dl considered as abnormal. Urine examined for presence microalbumin or more. Relationship between level of glycosylated haemoglobin and severity of diabetic retinopathy were assessed.

Based on clinical examination and result of blood urea, serum creatinine level correlation between various stages of diabetic retinopathy and diabetic nephropathy was determined.

Statistical Analysis

First all the data recorded in a Microsoft excel sheet and then statistical analysis was performed with the help of GraphPad Prism version (GraphPad software Inc., San Diego; 2007) software. Categorical variables were presented as number and percentage. Chi-square test has been done to find the association between different categorical variables. Significance of study parameters between two or more groups. For all statistical purpose P-value less than 0.05 considered as statistically significant.

RESULTS

This was a single center observational cross-sectional study done at one of the largest medical college of eastern India. During this study period 1209 confirmed case of diabetic mellitus attend our out-patient clinic for screening of diabetic retinopathy. Of them 273 (22.58 %) patient having clinical evidence of retinopathy were enrolled for this study. We are strictly followed the Helsinki declaration during the whole study period. In our study 148 (54.2 %) patients were male and remaining 125 (45.8 %) patients were females. The age of our study population ranges from 16 years to 73 years with the mean of 54.6 years. Mean duration of diabetes ranges from 2 years to 29 years with the mean of 7.4 years.

We divided all 272 patients according to their glycosylated haemoglobin level such as < 6 %, 6 – 8 % and more than 8 % to find the relationship between HbA1c and grade of diabetic retinopathy (table 1). Out of 273 patients only 20 (0.07 %) patients had glycosylated haemoglobin level less than 6 gm / dl, 82 (30 %) had 6- 8 gm % and remaining 170 (62.2 %) patients had glycosylated haemoglobin level more than 8 gram/dl.

Majority of the patients (73.6 %) had non-proliferative diabetic retinopathy, of them 93 had mild NPDR, 65 had moderate NPDR and 43 patients were suffering from severe non-proliferative diabetic retinopathy. Only 72 (26.4 %) patients had clinical features of proliferative diabetic retinopathy. We have observed that out of 93 patients of mild NPDR, 10 had HbA1c level < 6 %, 29 had HbA1c level between 6 – 8 % and 54 patients had HbA1c level more than 8 %.

Clinical Variables	Number of Patients Diagnosis					P Value
HbA1c level	**Mild NPDR**	**Moderate NPDR**	**Severe NPDR**	**PDR**	**Total**	
HbA1c < 6	10	8	2	1	**20**	< 0.001
HbA1c 6 - 8	29	34	7	12	**82**	
HbA1c > 8	54	23	34	59	**170**	
Total	**93**	**65**	**43**	**72**	**273**	

Table 1. Correlation of HbA1c with Severity of Diabetic Retinopathy

		Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Total	P Value
Blood Urea	< 40 mg / dl	64	31	14	25	**134**	< 0.001
	< 40 mg / dl	29	34	29	47	**139**	
Serum Creatinine	< 1.5 mg / dl	63	29	14	26	**132**	
	< 1.5 mg / dl	30	36	29	46	**141**	

Table 2. Correlation between Blood Urea, Creatinine with Severity of Diabetic Retinopathy

Out of 65 patients of moderate NPDR, 8 had HbA1c level < 6 %, 34 had HbA1c level between 6 – 8 % and 23 patients had HbA1c level more than 8 %. Out of 43 patients of moderate NPDR, 2 had HbA1c level < 6 %, 7 had HbA1c level between 6 – 8 % and 34 patients had HbA1c level more than 8 %. Out of 72 patients of moderate PDR, 1 had HbA1c level < 6 %, 12 had HbA1c level between 6-8 % and 59 patients had HbA1c level more than 8 %. On chi-Square test a statistically significant correlation exist between retinopathy and HbA1c level (p-value < 0.0001). Patients

were also divided according to their blood urea level such as less than 40 mg / dl and more than 40 mg / dl and find the relationship with grade of diabetic retinopathy (table 2).

Of these total 273 patient 139 (50.9 %) had blood urea level more than 40 mg /dl. The level of serum creatinine value was almost similar. Out of 273 patients 141 (51.6 %) had a serum creatinine level more than 1.5 mg/dl. We have observed that out of 93 patients of mild NPDR 64 patients had blood urea level < 40 mg / dl and 29 patients had blood urea level > 40 mg / dl. Out of 65 patients of moderate NPDR 31 had blood urea level < 40 mg / dl and 34 patients had blood urea level > 40 mg / dl. Out of 43 patients of severe NPDR 14 patients had blood urea level <40 mg/dl and 29 patients had blood urea level > 40 mg / dl. Out of 72 patients of proliferative diabetic retinopathy 25 had blood urea level < 40 mg / dl and 47 patients had blood urea level > 40 mg / dl. We were applied Chi-Square test to find a relationship between blood urea level and diabetic retinopathy grades and found a statistically significant relationship between then with an estimated p value of less than 0.001

A statistically significant association found between severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy and diabetic nephropathy with p-value less than 0.05.

DISCUSSION

Diabetes mellitus now is a major cause for both morbidity and mortality. As a metabolic disorder with high blood glucose, it ultimately affects our end organ like retina, kidney and leads to development of diabetic retinopathy and diabetic nephropathy. As we are able to see the retinal vasculature clinically so, severity of diabetic retinopathy will help us to estimating the presence of diabetic nephropathy. So, we can take timely steps to prevent the consequences of fatal diabetic nephropathy. A total of 1209 diagnosed patients attend our OPD clinic. Of them 273 (22.58 %) showed clinical signs of diabetic retinopathy. This result was almost similar to Chennai study where prevalence of diabetic retinopathy in diabetic population was 18.0 %. (95 % CI 16.0 - 20.1).[4] In a Spanish study 36.47 % patients of type 1 diabetes mellitus patients develop diabetic retinopathy; in type 2 diabetes patients' prevalence of diabetic retinopathy was 26.11 %.[12]

In the present study number of total study population were 273. Out of these 273 patients 148 (54.2 %) were male and remaining 125 (45.8 %) were female. Although the male population was slightly higher in our study, we did not find any significant prevalence difference between both the genders. Our result was consistent with the results published in various literatures. Henricsson M et al. found an equal prevalence of microvascular changes in both male and female.[13] The mean age of study population was 54.6 years with range from 16 to 73 years. Nivedita H et al.[14] observed the average age of study population was 62 years and average duration of diabetes mellitus was 6.9 years with a range of 2 - 28 years. In a Bangladeshi study 52 % patients were male and average age of the study population was 57.5 ± 10.9 years.[15] In a recent study by Ahmed MH et al. at Sudan average age of patients was 58.5 ± 10.7 years.[16] Romero-Aroca observed an average age of 47.16 ± 11.05 years with a range of 23 - 59 years. Here 52.72 % patients were female and 47.3 % were male.[17] Similar type of observation observed in a study done by Lee et al. here average age of the study population was 64.51 ± 11.47 years and 48.7 % of those were male.[18]

In our study out of 273 cases of clinically diagnosed diabetic retinopathy 93 (30.06 %) had mild NPDR, 65 (23.80 %) had moderate NPDR, 43 (15.75 %) severe NPDR and 72 (26.73 %) had proliferative diabetic retinopathy. In a study done at Bangladesh by Debnath et al. out of 100 patients 42% had NPDR, 24 % had PDR and remaining 34 % had diabetic retinopathy.[15] In 2010 Pedro RA et al. done a study at Spain where 26.11 % patients had DR and 6.74% had diabetic nephropathy.[12] Reddy et al. in India observed 12 (22.3 %) cases of mild NPDR, 16 (29.6 %) moderate NPDR, 16 (29.6 %) severe NPDR and 10 (18.5 %) cases of PDR in their 54 observed patients.[19] Nivedita H observed 50 patients, of them 46 % had moderate NPDR, 28 % mild NPDR, 16 % severe NPDR and in 10 % patients had PDR.[14]

In a study at Saudi Arabia by Aziz et al. out of 10580 cases diabetes 4655 patients had diabetic retinopathy. Of them 54.5 % patients suffered from NPDR, 25 % had moderate NPDR, 9 % had severe NPDR and almost 11.3 % patients suffered from proliferative diabetic retinopathy.[20] In our study number of PDR patient was slightly higher because our hospital is a tertiary care multispecialty referral medical college covering a large part of southern West Bengal. In this present study only 20 (7.32 %) patients had glycosylated haemoglobin less than 6 gm / dl. 82 (30.03 %) had HbA1c level between 6 - 8 gm / dl but remaining 170 (62.27 %) had HbA1c level more than 8 gm / dl. In our study high Hb1Ac (> 8 %) seen in 79 % patients of severe non-proliferative diabetic retinopathy and 81.9 % patient with proliferative diabetic retinopathy.

Patients with poor glycaemic control are more likely to develop diabetic retinopathy and nephropathy. DCCT study showed 76 % reduced chance of development of any new diabetic retinopathy and 80 % chance of reduction in the progression of established retinopathy in patients with strict control of hyperglycemia.[21] A positive correlation between the severity of retinopathy and the high level of HbA1c after 10 years of diabetes mellitus was established in Wisconsin epidemiological study.[22] The UKPDS study suggest that with every 1 % decrease in HbA1c risk of development of diabetic retinopathy was reduced by 19 %.[23] Our study clearly indicates that poor control of Hb1Ac associated with increasing prevalence of severe NPDR and PDR. In our study, 29 (31.1 %) mild NPDR, 34 (52.3 %) moderate NPDR, 29 (67.4 %) severe NPDR and 47 (65.2 %) PDR patient had blood urea level more than 40 mg / dl. We use serum creatine value of more than 1.5 mg / dl as an indicator for diabetic nephropathy. Here 30 (32 %) mild NPDR, 36 (55.4 %) moderate NPDR, 29 (67.4 %) severe NPDR and 46 (63.9 %) PDR patient had serum creatinine value of more than 1.5 mg/dl.

In our study among 273 patients with diabetic retinopathy 139 (50.09 %) patients had blood urea > 40 mg / dl, where 141 (51.64 %) had serum creatinine more than

1.5 mg / dl. we found a positive correlation between severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy and diabetic nephropathy ($P < 0.05$). In Debnath study out of 100 patients 64 had diabetic nephropathy and 66 had diabetic retinopathy.[15] Aziz et al. also suggest that presence of diabetic retinopathy in diabetic population increases the chances of diabetic nephropathy.[20] According to Jeng in Taiwan among diabetic patient with diabetic nephropathy had 5 times more chances to develop diabetic retinopathy.[24] In a small study in India Reddy et al. observed out of 54 patients with diabetic retinopathy 28 (51.8 %) had diabetic nephropathy and remaining 26 (48.2 %) had no diabetic nephropathy.[19] M.H. Ahmed et al. observed patient with diabetic retinopathy had 35.6% chances to develop diabetic retinopathy.[16] Lee suggested significant association between diabetic retinopathy and diabetic nephropathy in the univariate X^2 test.[18] It was observed that diabetic retinopathy independently associated with development of microalbuminuria and it's a strong predictor for development of diabetic nephropathy in diabetic population.[25] Villar et al. also demonstrated that presence of diabetic retinopathy is a very important factor for development diabetic nephropathy.[26]

CONCLUSIONS

Patients whose glycosylated haemoglobin was more than 8 % have high chance of developing diabetic retinopathy and diabetic nephropathy. A significant number of patients with severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy had a higher level of blood urea and serum creatine level as compared to patient with mild or moderate NPDR. It indicates prevalence of diabetic nephropathy is more common in severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy and shows a significant connection between advanced diabetic retinopathy and diabetic nephropathy.

Detection of diabetic retinopathy can be done by simple clinical examination and it is done in every ophthalmological set up. As microvascular changes in retina co-relate with microvascular changes in kidney hence early detection of diabetic retinopathy can help us to take timely taken steps to prevent end stage renal disease.

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