Study of Correlation between Renal Function Test and Severity of Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND

Retinopathy and nephropathy are chronic vascular complications of type 2 diabetes mellitus, this eventually leads to end stage renal disease and blindness. Diabetic retinopathy is an important cause of legal blindness in 20 - 70 years. The purpose of the study was to establish association between severity of diabetic retinopathy with systemic levels of glycosylated haemoglobin and renal function test.

METHODS

This is a cross sectional study conducted among 75 patients with type 2 diabetes mellitus attending the ophthalmology out-patient department (OPD) of Acharya Vinoba Bhave Hospital, Wardha and patients referred from the hospital. Detailed fundus examination and staging of diabetic retinopathy (DR) was done. Glycosylated haemoglobin levels, serum creatinine and blood urea nitrogen were measured.

RESULTS

Majority of patients were in the age range of 61 to 70 years. Mean ± SD of 3 parameters in patients with no DR, mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR and proliferative diabetic retinopathy (PDR) were as follows: Serum creatinine 1.12 ± 0.41, 1.21 ± 0.53, 1.35 ± 0.49, 1.55 ± 0.22 and 1.70 ± 0.23 respectively. P = 0.007. Blood urea nitrogen (BUN) 28.62 ± 4.20, 31.83 ± 7.20, 37.31 ± 12.57, 44.21 ± 7.53 and 48.76 ± 5.08 respectively. P = 0.0001. HbA1c l, 6.72 ± 0.60, 8.14 ± 0.98, 8.52 ± 2.67, 9.96 ± 1.22 and 12.14 ± 1.96 respectively. P = 0.0001. All the 3 parameters were statistically significant. 40 % of cases had clinically significant macular oedema.

CONCLUSIONS

Poor glycaemic control as seen by higher levels of glycosylated haemoglobin and deranged renal function is associated with severe form of DR.

KEY WORDS

Diabetes Mellitus, Diabetic Retinopathy, Serum Creatinine HbA1c and BUN

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BACKGROUND

Diabetes mellitus (DM) is a metabolic disease caused by hereditary and environmental factors characterized by hyperglycaemia. The biochemical dysfunction in diabetes leads to various microvascular and macrovascular complications like nephropathy, retinopathy, neuropathy, atherosclerosis etc.[1] It has been estimated that 30 % of people with DM have diabetic retinopathy worldwide.[2] Its incidence is very high in Indian population. India comprises a largest hub of diabetics, with 31.7 million cases of type 2 DM and a three - fold rise in disease prevalence in rural (2 - 6 %) and urban (5 - 15 %) areas.[3]

World Health Organization (WHO) reports indicate that India tops the world with the largest number of diabetic subjects.[4] India ranks second place in top ten countries with the highest number of diabetic patients in the 20 - 79 years age group (72.9 million).[5] Diabetic retinopathy and nephropathy are serious end stage complications of diabetes mellitus. Diabetic retinopathy is the most common ocular complication of diabetes.[6] The overall prevalence of DR of any severity is 34.6 % and the prevalence of proliferative diabetic retinopathy and diabetic macular oedema (DME) is 6.96 % and 6.81 % respectively.[2] Elevated level of glucose plays major factor for diabetic microangiopathy. Various metabolic pathways like polyol pathway, advanced glycation end products accumulation, protein kinase C pathway and hexosamine pathway are involved in hyperglycaemic induced vascular destruction.

The earliest responses of the retinal blood vessels are dilatation of blood vessels and changes in the blood flow. Pericyte loss is also an early change in DR. Pericyte provide structural support to the capillaries but their loss leads to localized outpouching of the capillary walls which eventually forms microaneurysms. Also, apoptosis of endothelial cells and thickening of basement membrane contribute towards blood retinal barrier impairment. Further marked pericyte and endothelial cell loss results in capillary occlusion and ischemia. Under diabetic condition and retinal ischaemia / hypoxia upregulation of vascular endothelial growth factor (VEGF) occur by activation of hypoxia inducible factor 1 and also by phospholipase A2. VEGF are also believed to increase phosphorylation of tight junction proteins such as zonula occludens -1, this leads to progression of PDR and DME.

Diabetic retinopathy is classified into non-proliferative DR and proliferative DR. Most patients of PDR have had NPDR for a few years at least prior to developing the proliferative form. Non-proliferative diabetic retinopathy is characterized by presence of micro-aneurysms, intra-retinal haemorrhages, cotton-wool spots, venous beading & loops, intraretinal microvascular abnormalities (IRMA) and hard exudate.

NPDR is subdivided into mild, moderate, and severe depending on retinal quadrants involved.

Mild NPDR

Any or all of: microaneurysms, retinal haemorrhages, exudates, cotton wool spots, up to the level of moderate NPDR. No intraretinal microvascular anomalies (IRMA) or significant beading.

Moderate NPDR

Severe retinal haemorrhages in 1–3 quadrants or mild IRMA, significant venous beading can be present in no more than 1 quadrant and cotton wool spots commonly present

Severe NPDR

The 4–2–1 rule; one or more of: Severe haemorrhages in all 4 quadrants, significant venous beading in 2 or more quadrants, moderate IRMA in 1 or more quadrants.

Proliferative diabetic retinopathy is characterized by neovascularization of retina, disc, iris or angle, pre-retinal or vitreous haemorrhages, tractional retinal detachment.

Mild-Moderate PDR

New vessels on the disc (NVD) or new vessels elsewhere (NVE), but extent insufficient to meet the high-risk criteria.

High Risk PDR

New vessels on the disc greater than early treatment diabetic retinopathy study (ETDRS) standard photograph 10A (about 13-disc area)

- Any NVD with vitreous haemorrhage
- NVE greater than 12-disc area with vitreous haemorrhage advanced diabetic.

Diabetic macular oedema is a thickening of the central part of the retina, the macula that may affect people with diabetic retinopathy. Clinically significant macular oedema (CSME) is defined as retinal thickening at or within 500 μ of the center of macula, hard exudates at or within 500 μ of the center of macula with adjacent retinal thickening and retinal thickening of 1 disc diameter (DD) or larger any part of which is within 1 DD of the center of the fovea.

Diabetic nephropathy presents with elevated arterial blood pressure, albuminuria, decrease in glomerular filtration rate with increase of cardiac abnormalities. Path mechanism of DR and nephropathy is similar. Patients with DR have nephropathy and vice versa. Changes in retinal vasculature can be directly visualized by ocular fundus imaging modalities like fundus photography, fundus fluorescein angiography and optical coherence tomography but not the renal vasculature. Hence, estimation of renal function test (RFT) is required for monitoring the kidney function. Glycosylated haemoglobin level is a method for estimating the degree of hyperglycaemia over a period of 2 to 3 months.[7,8] HbA1C has become the gold standard for the therapeutic management of diabetes mellitus in research and in the clinical setting.[9]

The purpose of the present study was to find out correlation between levels of HBA1c & RFTs with the severity of DR in patients with type 2 DM.

METHODS

The study was rural hospital based cross sectional study conducted between June 2020 to November 2020 in the

Department of Ophthalmology at Acharya Vinoba Bhave Rural Hospital attached to Jawaharlal Nehru Medical College, Sawangi (Meghe) Wardha, a constituent college of Datta Meghe Institute of Medical Sciences (Deemed to be University), Nagpur. Informed consent was obtained from all subjects. The study was approved by the Ethics and Research committees of DMIMS (DU) and was carried out in accordance with the tenets of the Declaration of Helsinki.

For this, 75 patients with diagnosed and / or admitted with type 2 DM were sequentially included in the study attending the ophthalmology OPD / IPD at AVBRH after taking the inclusion and exclusion criteria into consideration.

Inclusion Criteria

1. Diagnosed with type 2 DM.
2. No other systemic illness.
3. Age group: 30 - 90 years

Exclusion Criteria

1. Ocular comorbidities like glaucoma, any other retinal pathologies.
2. Ocular trauma
3. Systemic illnesses affecting retina like hypertensive retinopathy.
4. Cataract with pseudoexfoliation or posterior synechiae.
5. Any other kidney disease
6. Patients not giving informed consent.

All patients underwent detailed fundus examination with indirect ophthalmoscopy and slit lamp biomicroscopy VOLK double aspheric +90D lens by vitreoretinal specialist and stage of DR with presence or absence of CSME. Laboratory tests done were blood urea nitrogen, serum creatinine level and HbA1c by Vitros 5600 of ortho clinical diagnostic.

Statistical Analysis

Statistical analysis was done by using descriptive and inferential statistics using one-way analysis of variance (ANOVA) and software used in the analysis was SPSS 24.0 version and $P < 0.05$ is considered as level of significance.

RESULTS

Total 75 patients with type 2 DM were included in the study. Age ranged from 30 to 90 years and mean age of the patients was 59.16 ± 10.91 years. Majority of patients were in the range of 61 to 70 years (56.36 %). Gender wise, 42 were male and 33 were female. There was no statistically significant difference for age and gender with respect to severity of DR. Mean duration of DM ranged from 4 to 24 years. Out of 75 patients, (10.67 %) had no DR, (24 %) mild NPDR, (29.33 %) moderate NPDR, (18.67 %) severe NPDR and (17.33 %) PDR.

Mean ± SD of serum creatinine level in patients with no DR, mild NPDR, moderate NPDR, severe NPDR and PDR were 1.12 ±0.41, 1.21 ±0.53, 1.35 ±0.49, 1.55 ± 0.22, and 1.70 ±0.23 respectively. P value was 0.007. The difference was statistically significant. (Table 1) Mean ± SD of BUN level in patients with no DR, mild NPDR, moderate NPDR, severe NPDR and PDR were 28.62 ±4.20, 31.83 ± 7.20, 37.31 ± 12.57, 44.21 ± 7.53 and 48.76 ± 5.08 respectively. P value was 0.0001. The difference was statistically significant. (Table 2).

Type of DR	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum	F - Value
No DR	8	1.12	0.41	0.14	0.60	1.90	
Mild NPDR	18	1.21	0.53	0.12	0.50	2.10	
Moderate NPDR	22	1.35	0.49	0.10	0.80	2.60	3.88 P = 0.007, S
Severe NPDR	14	1.55	0.22	0.05	1.20	1.90	
PDR	13	1.70	0.23	0.06	1.20	2.10	
Total	**75**	**1.39**	**0.45**	**0.05**	**0.50**	**2.60**	

Table 1. Association of Serum Creatinine with Severity of DR

Type of DR	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum	F - Value
No DR	8	28.62	4.20	1.48	21.00	35.00	
Mild NPDR	18	31.83	7.20	1.69	20.00	42.00	
Moderate NPDR	22	37.31	12.57	2.68	18.00	68.00	11.18 P = 0.0001, S
Severe NPDR	14	44.21	7.53	2.018	35.00	62.00	
PDR	13	48.76	5.08	1.417	40.00	56.00	
Total	**75**	**38.34**	**10.91**	**1.26**	**18.00**	**68.00**	

Table 2. Association of Blood Urea Nitrogen to Severity of DR

However, in 23.07 % of patients with PDR and 14.28 % of severe NPDR, BUN and serum creatinine level were normal. 12.5 % of patients with mild and moderate NPDR, BUN and serum creatinine level were higher. Mean ± SD of HbA1c level in patients with no DR, mild NPDR, moderate NPDR, severe NPDR and PDR were 6.72 ± 0.60, 8.14 ± 0.98, 8.52 ± 2.67, 9.96 ± 1.22 and 12.14 ± 1.96 respectively. P value was 0.0001. The difference was statistically significant. (Table 3). 40 % of cases had clinically significant macular oedema according to our study. All these cases had higher level of BUN, serum creatinine HbA1c levels.

Type of DR	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum	F - Value
NO DR	8	6.72	0.60	0.21	6.10	7.70	
Mild NPDR	18	8.14	0.98	0.23	6.20	9.86	
Moderate NPDR	22	8.52	2.67	0.56	4.20	14.00	14.86 P = 0.0001, S
Severe NPDR	14	9.96	1.22	0.32	8.10	12.80	
PDR	13	12.14	1.96	0.54	8.10	14.30	
TOTAL	**75**	**9.14**	**2.42**	**0.27**	**4.20**	**14.30**	

Table 3. Association of HbA1c to Severity of DR

DISCUSSION

Diabetic retinopathy is common ocular manifestation in patients with diabetes of duration more than 10 years or more. Both diabetic retinopathy and nephropathy are microvascular complication of diabetes. If not detected early, can lead to blindness and renal failure. Patients with DR usually are not aware in early stage of the disease since there is no visual disturbance. Hence, screening of all diabetics for retinal examination and renal function test are important to prevent complications.

Patients with poor glycaemic control as estimated by HbA1c level value > 8 % are at high risk of developing diabetic nephropathy and DR[10]. DCCT showed 76 % reduction in the rate of development of any retinopathy and an 80 % reduction in progression of established retinopathy in patients with strict control of diabetes.[10] Renal malfunction in diabetics is a risk factor for progression and deterioration of diabetic retinopathy.[11] Wisconsin epidemiological study of diabetic retinopathy showed a positive correlation between severity of retinopathy and high level of HbA1C after 10 years of diabetes mellitus.[9] Our study included total 75 patients with type 2 DM, mean age of the patients was 59.16 ± 10.91 years, 42 were male and 33 were female. Mean duration of DM ranged from 4 to 24years. Mean ± SD of serum creatinine level in patients with no DR, mild NPDR, moderate NPDR, severe NPDR and PDR were 1.12 ±0.41, 1.21 ± 0.53, 1.35 ±0.49, 1.55 ± 0.22, and 1.70 ±0.23 respectively. P value was 0.007. The difference was statistically significant.

Mean ± SD of BUN level in patients with no DR, mild NPDR, moderate NPDR, severe NPDR and PDR were 28.62 ±4.20, 31.83 ± 7.20, 37.31 ± 12.57, 44.21 ± 7.53 and 48.76 ± 5.08 respectively. P value was 0.0001. The difference was statistically significant. Findings in our study were comparable to other studies[7,12] but in Tamadon MR et al.[13] study serum creatinine level showed no correlation with severity of DR. However, in 23.07 % of patients with PDR and 14.28 % of severe NPDR, BUN and serum creatinine level were normal. 12.5 % of patients with mild and moderate NPDR, BUN and serum creatinine level were higher. Mean ± SD of HbA1c level in patients with no DR, mild NPDR, moderate NPDR, severe NPDR and PDR were 6.72 ± 0.60, 8.14 ± 0.98, 8.52 ± 2.67, 9.96 ± 1.22 and 12.14 ± 1.96 respectively. P value was 0.0001. The difference was statistically significant. This is comparable to other studies.[1,7,9] In our study, 40 % of cases had clinically significant macular oedema. All these cases had higher level of BUN, Serum creatinine and HbA1c levels.

CONCLUSIONS

Diabetic retinopathy in severe form can be potentially blinding. Renal malfunction i.e. raised BUN and serum creatinine have positive relation with the severity of retinopathy as seen in our study. However, some patients may have no or milder form of DR but deranged RFT or may be vice versa. But nephropathy and retinopathy are closely associated in DM. Similarly, higher level of glycosylated haemoglobin is associated with severe form of retinopathy as seen in our study. Thus, decreasing level of HbA1c along with good glycaemic control and monitoring level of RFTs and periodic evaluation for retinopathy can postpone or prevent blindness due to retinopathy.

Limitations

- Small sample size
- Other parameters like lipid profile, liver function test (LFTs), blood pressure (BP) were not considered.
- Microalbuminuria was not included.

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