

Prevalence of systemic co-morbidities in patients with various grades of diabetic retinopathy

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Background & objectives: Though diabetes affects multiple organs, most studies highlight the occurrence of only one complication in isolation. We conducted a hospital-based study to estimate the co-existence of significant systemic co-morbid conditions in patients with varying grades of diabetic retinopathy.

Methods: A total of 170 consecutive patients with diabetic retinopathy were prospectively recruited for the study between June 2009 to June 2010 at a tertiary care eye centre in north India. Retinopathy was graded by fundus biomicroscopy and fundus photography and classified into three categories (mild-moderate nonproliferative retinopathy, proliferative retinopathy requiring only laser and proliferative retinopathy requiring surgery). Nephropathy was classified by calculating the six variable estimated glomerular filtration rate (eGFR) for all patients. Nerve conduction studies and clinical assessment were used to determine presence of neuropathy. Co-existence of macrovascular disease and peripheral vascular disease was also ascertained.

Results: The percentages of patients with overt nephropathy in the three groups were 19.2, 38.0 and 41.2, respectively. Significant linear trends were observed for serum creatinine ($P=0.004$), albumin ($P=0.017$) and eGFR ($P=0.030$). A higher per cent had abnormal nerve conduction on electrophysiology than that diagnosed clinically (65.4 vs. 44.2, 76.0 vs. 40.0 and 64.8 vs. 48.6, respectively). The odds ratio (95% CI) for co-existence of nephropathy, neuropathy, CVA (cerebrovascular accidents) and PVD (peripheral vascular disease) was 2.9, 0.9, 4.8 and 3.5, respectively. Independent of retinopathy severity, patients with clinically significant macular oedema (CSME) had a higher percentage of nephropathy ($P < 0.005$).

Interpretation & conclusions: The co-existence of overt nephropathy, nerve conduction based neuropathy and macrovascular co-morbidity in patients with early grades of diabetic retinopathy was significant. Screening for overt nephropathy by eGFR should be considered in all patients with clinically significant macular oedema.

Key words Diabetes mellitus - GFR - microalbuminuria - nephropathy - neuropathy - retinopathy

The number of people worldwide who have diabetes mellitus (DM) is expected to increase to almost 300 million by the year 2025¹. Diabetes can affect multiple organs in the body and the risk of complications increases with disease duration. After 20 years nearly 99 per cent of patients of type 1 and about 60 per cent of type 2 diabetes mellitus develop some grade of retinopathy². Diabetes has become the most common single cause of end-stage renal disease (ESRD), accounting for over one-third of all patients who are on dialysis. Approximately 25 to 40 per cent of patients with DM type I, and 20-30 per cent of DM type II ultimately develop diabetic nephropathy^{3,4}. Nephropathy progresses sequentially from stage 1 (very early diabetes) to stage 5 (ESRD) and without specific interventions, 80 per cent of stage 2 patients will evolve to stage 3 over a period of 10-15 years⁵⁻⁶. About 60 to 70 per cent people with diabetes have some form of neuropathy⁷. Cardiovascular disease is increased in individuals with type 1 or type 2 DM. The Framingham heart study revealed diabetes mellitus to be a major risk factor for cardiovascular disease⁸.

Patients with one microvascular complication are likely to have a higher incidence of other micro- and macro-vascular complications. These complications increase the risk of mortality and cause a profound economic burden⁹. Previous studies have reported the presence of a single or only a few complications in diabetic patients¹⁰⁻²³.

This hospital-based study, carried out at an apex eye centre in New Delhi, India reports the occurrence of nephropathy, neuropathy, cardiovascular disease, cerebrovascular disease and peripheral vascular disease in a group of diabetic retinopathy patients.

Material & Methods

The study was carried out at Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences (AIIMS), New Delhi, India between June 2009 and June 2010. A total of 170 consecutive patients (105 men and 65 women) with diabetic retinopathy were prospectively recruited for the study. All patients were diagnosed with diabetes mellitus and had established retinopathy. Patients were prospectively recruited from the medical retina clinic and inpatient admissions (for surgery) in the retina unit of this tertiary care hospital. The study was approved by the Institute Ethics committee, and each subject provided written informed consent before the start of the study. The

main inclusion criterion for the study was patients with pre-existing or newly diagnosed diabetic retinopathy. Patients with other retinal disorders like retinal vascular occlusion, age related macular degeneration were excluded. Subjects were categorized into three groups based on the severity of retinopathy [Group 1 (NP, n=52): Mild-moderate non-proliferative retinopathy, Group 2 (PNS, n=50): Proliferative retinopathy (not requiring surgery), Group 3 (PS, n=68): Patients admitted for diabetic vitreoretinal surgery].

Severity of diabetic retinopathy was determined by fundus biomicroscopy and/or retinal photography. The Early Treatment of Diabetic Retinopathy Study (ETDRS) classification for diabetic retinopathy grading was followed²⁴. For identification of nephropathy, the six variable estimated glomerular filtration rate (eGFR) was calculated for all the patients. (eGFR is a function of the patient's age, gender, ethnicity, blood urea, serum creatinine and serum albumin). The Chronic Kidney Disease (CKD) classification²⁵, based on eGFR and presence/ absence of microalbuminuria, was used to grade nephropathy (grades 1-5). In case of any evidence of nephropathy, obstructive disorders were ruled out by an abdominal ultrasound. Presence and pattern of diabetic neuropathy was determined by nerve conduction studies and clinical evaluation of sensory/motor and autonomic systems. VikingSelect™ (Nicolet biomedical™, Madison WI, USA) was used for nerve conduction velocity (NCV) analysis. For the upper limb, conduction was checked in the median and ulnar motor and sensory nerves. For the lower limb, motor nerve conduction was checked in the peroneal and tibial nerves, while sural nerves were used for sensory testing. Presence of cardiac disease was determined by history of an episode of angina/ myocardial infarction and procedures of cardiac angiography/angioplasty. The cardiac risk profile was assessed taking account of obesity, hypertension, hyperlipidaemia, pedal oedema, history of smoking, family history of cardiovascular disease, blood pressure, chest X-ray and changes on ECG. Further evaluation was undertaken (e.g. stress testing, echocardiography) in the event of multiple risk factors or presence of abnormalities in the above tests. Presence of cerebral and peripheral vascular disease was elicited by history of mild/ major stroke and of gangrene/amputation, respectively.

Statistical analysis was performed after compilation of data using SPSS (version 15.0, Chicago IL, USA) for descriptive and comparative results. Arithmetic

mean, standard deviation and frequency distribution were calculated for all the descriptive parameters. Chi-square test was used to determine the significance of association between a categorical risk factor and a given diabetes complication. For risk factors measurable on an interval scale, comparisons were made using Students' t-test. In case of large range, variation and small number of observations, the data were compared using non parametric tests like Mann-Whitney test and Kruskal-Wallis test. Cornfields' odds ratios were computed to examine the estimated relative risk of each complication with staged severity of retinopathy. The significance of associations between retinopathy severity level and the occurrence of other diabetic complications was examined using the chi-square test.

Results

A total of 170 patients with diabetic retinopathy were assessed and grouped depending on the severity of retinopathy. There were 52 patients with mild-moderate non-proliferative diabetic retinopathy, NPDR (group NP), 50 with PDR not requiring surgery (group PNS) and 68 patients with PDR who were undergoing vitreoretinal surgery for a complication ensuing from diabetic retinopathy (group PS).

The baseline characteristics of various parameters between the three groups are shown in Table I. The mean age of the subjects was 54 yr; 62 per cent were males and 38 per cent were females. There were eight patients with type 1 and 162 with type 2 diabetes. The mean duration of diabetes mellitus was 12.17 yr.

The best corrected visual acuity (BCVA) proportionately decreased with increase in severity of diabetic retinopathy. The log MAR (logarithm of minimum angle of resolution) BCVA values in the three groups were (mean \pm S.D.; R,L)- NPDR, 0.50 \pm 0.53, 0.51 \pm 0.46; PDR not requiring surgery, 1.07 \pm 0.76, 0.84 \pm 0.5 and PDR requiring surgery, 1.56 \pm 0.70, 1.64 \pm 0.62; overall $P < 0.001$. In the surgical group, the indications for surgery were (% of all) tractional retinal detachment - 39, vitreous haemorrhage- 26, subhyaloid haemorrhage-25, combined tractional-rhegmatogenous retinal detachment - 6 and neovascular glaucoma - 3.

The percentage of patients with overt nephropathy (CKD grade \geq 3) in the three groups were 19.2, 38.0 and 41.2, respectively, ($P=0.030$). Significant linear trends were observed for serum creatinine ($P=0.004$), serum albumin ($P=0.017$) and eGFR ($P=0.030$). The difference was most marked between groups NP and PS for each of the above parameters. A comparison of the quantitative nephropathy parameters between the various groups of retinopathy is shown in Table II. Between the groups with duration of DM \leq 5, >5-10 and >10 yr, the renal function declined progressively, the mean eGFR were 95.4, 74.1 and 80.9. There was a significant reduction of eGFR when values in subjects with duration of disease \leq 5 yr was compared to those with 5-10 yr ($P=0.034$) or >10 yr ($P=0.041$).

In each of the three groups, a higher percentage of patients had neuropathy based on abnormal nerve conduction on electrophysiology than those diagnosed clinically (65.4 vs. 44.2, 76.0 vs. 40.0 and 64.8 vs. 48.6,

Table I. Baseline characteristics of study subjects

Parameter	NPDR group 1 (NP) (n=52)	PDR not requiring surgery group 2 (PNS) (n=50)	PDR requiring surgery group 3 (PS) (n=68)	Combined (n=170)	<i>P</i> value
Age (yr)	54.2 (8.4)	55.46 \pm 9.4	52.49 \pm 7.3	53.9 \pm 8.3	0.15
Gender (M:F)	30 (57.7): 22 (42.3)	34 (68.0): 16 (32.0)	41 (60.3): 27 (39.7)	105 (61.8): 65 (38.2)	0.53
BMI (kg/m ²)	23.4 \pm 2.8	24.3 \pm 4.2	23.9 \pm 3.3	23.9 \pm 3.4	0.459
HbA _{1c} (%)	8.6 \pm 1.6	7.77 \pm 1.4	7.76 \pm 1.4	8.04 \pm 1.5	0.002
On OHA	38 (73.1)	26 (52.0)	28 (41.8)	92 (54.4)	0.003
On insulin	14 (26.9)	24 (48.0)	39 (58.2)	77 (45.6)	
Duration of diabetes (yr)	10.39 \pm 5.7	14.48 \pm 10.02	11.48 \pm 7.6	12.17 \pm 7.9	0.032
Type I	2 (3.8)	2 (4.0)	4 (5.9)	8 (4.7)	0.84
Type II	50 (96.2)	48 (96.0)	64 (94.1)	162 (95.3)	

Values in parentheses are percentages
NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; OHA, oral hypoglycaemic agent

Table II. Comparison of nephropathy parameters with severity of retinopathy. All values are represented as mean (SE)

Nephropathy parameters (mean values)	NPDR (n=52)	PDR not requiring surgery (n=50)	PDR requiring surgery (n=68)	Combined (n=170)	<i>P</i> value
Creatinine (mg %)	1.09 ± 0.07	1.28 ± 0.1	1.78 ± 0.2	1.42 ± 0.1	0.004
Urea (mg %)	41.7 ± 4.2	45.3 ± 3.9	53.7 ± 3.2	47.6 ± 2.2	0.053
Albumin (mg %)	4.16 ± 0.05	4.08 ± 0.06	3.92 ± 0.06	4.04 ± 0.04	0.017
eGFR (ml/min)	95.2 ± 5.1	80.2 ± 4.7	75.5 ± 5.8	82.9 ± 3.2	0.030

NPDR, non proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy

respectively). The presence of neuropathy (based on electrophysiology) also increased progressively (50.0, 65.1, 79.5 respectively; $P=0.003$).

The per cent of other co-morbidities in the three groups is shown (Table III). Except for the rate of CVA, which was higher in patients with PDR requiring surgery ($P=0.045$), there was no significant difference in the frequency of other macrovascular co-morbidities between the groups. Among the macrovascular diseases, there was a significant rise in the per cent of cases with peripheral vascular disease (2.3, 11.6 and 19.3, respectively; $P=0.024$) (Table IV). No significant difference was seen for the other macrovascular co-morbidities.

A sub-analysis of group NP was done with respect to the presence or absence of clinically significant nuclear oedema (CSME). The mean values of blood urea and serum creatinine were higher in those with CSME than those without (47.1 vs. 29.8 mg%, $P=0.004$; 1.1 vs. 0.9 mg%, $P=0.67$, respectively). The eGFR showed a direct inverse relation and was significantly lower in those with CSME than those without CSME (88.4 vs. 110.7 ml/min, $P=0.036$). Likewise, the percentage of patients with overt nephropathy increased in those with CSME from those without CSME (25.0 vs. 6.3%) but

fell short of significance. The presence of neuropathy (based on electrophysiology) increased significantly in patients with CSME when compared to those without CSME (77.8 vs. 37.5%, $P=0.005$). Associated hypertension and hyperlipidaemia in the two groups was 66.7 vs. 37.5 per cent, $P=0.049$ and 38.9 vs. 18.8, $P=0.141$; respectively.

The patients were also stratified based on the duration of diabetes to ≤ 5 , 5-10 and >10 yr, and a comparative analysis for co-existence of microvascular and macrovascular complications was done. Results are summarized in Table IV. The percentage of patients with NPDR, PDR not requiring surgery and PDR requiring surgery in subjects with duration of disease less than 5 yr was 22.7, 36.4 and 40.9, respectively. The distribution for subjects with 5-10 yr duration was 46.5, 13.9 and 39.5; and for subjects with more than 10 years- 26.5, 33.7 and 39.8, respectively. A high proportion of patients with ≤ 5 yr diabetes duration was also noted to have advanced PDR that required surgery.

Discussion

Our results highlight the widespread co-existence of microvascular and macrovascular co-morbidities in

Table III. Comparison of macrovascular risk factors/disease between groups

Co-morbidity	NPDR (n=52)	PDR not requiring surgery (n=50)	PDR requiring surgery (n=68)	Combined (n=170)	<i>P</i> value
HTN	57.7	68.0	69.1	65.3	0.382
HYL	32.7	44.0	41.2	39.4	0.469
CVD	23.1	20.0	25.0	22.9	0.815
CVA	3.8	6.0	16.2	9.4	0.045
PVD	5.8	14.0	17.6	12.9	0.153

Values given as % age of patients in each group
HTN, hypertension; HYL, hyperlipidaemia; CVD, cardiovascular disease; CVA, cerebrovascular disease; PVD, peripheral vascular disease

Table IV. Comparison of micro- and macro-vascular complications with duration of diabetes mellitus (% of patients)

Duration of DM (yr) (% prevalence)	Neuropathy	Nephropathy	HTN	HYL	CVD	CVA	PVD
≤5 (n=44)	50.0	25.0	63.6	45.5	15.9	2.3	2.3
>5-10 (n=43)	65.1	41.9	69.8	30.2	23.3	11.6	11.6
>10 (n=83)	79.5	33.7	63.9	41.0	26.5	12.0	19.3
<i>P</i> value	0.003	0.25	0.775	0.321	0.4	0.17	0.024

HTN, hypertension; HYL, hyperlipidaemia; CVD, cardiovascular disease; CVA, cerebrovascular disease; PVD, peripheral vascular disease

patients with even early grades of diabetic retinopathy. Of the microvascular complications, high occurrence of both overt nephropathy and neuropathy (based on nerve conduction studies) was found. Hypertension, hyperlipidaemia, cardiovascular disease and cerebrovascular events were also observed in all patients, strikingly even in those with non-proliferative stage of the disease. Peripheral vascular disease showed a rising but non significant trend.

Some studies have demonstrated retinopathy to be strongly associated with diabetic nephropathy, with or without increased blood pressure²⁵⁻²⁹. El-Asrar and colleagues³⁰ have reported that the prevalence of diabetic nephropathy increases with increasing severity of diabetic retinopathy. Recent data from an Indian population study observed that the odds ratios for presence of nephropathy in those with NPDR without macular oedema and in those with sight threatening retinopathy, were 2.3 and 5.3, respectively in comparison to those with no retinopathy³¹. However, other studies have found pronounced discordance between the severity of nephropathy and diabetic retinopathy. We observed a high percentage of overt nephropathy in all patients. The percentage of nephropathy observed in our study in patients with NPDR was higher than that that reported by El-Asrar *et al*³⁰. In our study univariate analyses indicated that patients with PDR undergoing medical/laser treatment and those undergoing surgery were 2.5 and 2.9 times as likely to have nephropathy as those with mild-moderate NPDR.

Since the presence of macular oedema has often been regarded as a risk factor/ marker of systemic imbalance, a sub-analysis was done in the NPDR group. This revealed higher values of urea and lower eGFR in those with CSME. This corroborated with an

earlier report of association of macular oedema with nephropathy³². eGFR seems to be an important marker of renal dysfunction as changes are detected earlier than an evident rise in creatinine.

Previous reports have emphasized on the frequent occurrence of abnormal nerve conduction in absence of clinical neuropathy in patients with type 1 DM^{33,34}. One study found at least two abnormal independent neurophysiologic nerve parameters in upto 96.6 per cent of 30 diabetic patients who were all clinically asymptomatic³⁴. The CURES study³¹ used the vibratory perception threshold of big toe > 20mV as the marker of neuropathy and reported the prevalence to be 28.4 per cent for NPDR without macular oedema and 47.5 per cent for sight threatening retinopathy. We found a high percentage neuropathy in all patients with some form of retinopathy, relative to the reported prevalence in diabetic populations without retinopathy. Nerve conduction studies detected more patients to be having neuropathy than diagnosed clinically even in those with early stages of retinopathy. Subgroup analysis revealed that within the NPDR group, those with CSME had a significantly higher probability of coexisting neuropathy.

In our study, the percentage of patients with any cerebrovascular accident was 3.8 per cent in patients with NPDR and increased to 16.2 per cent in those with advanced retinopathy. Our observation supported the high incidence of cerebrovascular disease even in those with early retinopathy, and the risk was significantly higher in the proliferative stage. Autopsy studies have shown that the increased risk of ischemic stroke in diabetes is a result of occlusion of small paramedian penetrating arteries and not carotid disease and that the vascular lesions in the small vessels of the brain are proliferative lesions^{35,36}. This supports our observation that diabetic subjects with retinopathy, especially

proliferative retinopathy appear to be at a high risk of ischaemic strokes.

Diabetes increases the risk of macrovascular complications, which can lead to a 10–15 times higher risk of lower extremity amputation and ischaemic heart disease. Several prospective studies have documented a higher cardiovascular morbidity/ mortality in those with diabetic retinopathy, especially in the proliferative stage, in patients with diabetes mellitus, independent of other known risk factors³⁰. In our study, hypertension, hyperlipidaemia, CVD and peripheral vascular disease were observed in a high proportion of patients.

Limitations of our study include the small sample size and the failure to include a group of diabetes patients with no retinopathy. Also, this being a hospital-based study in a tertiary care set up a large proportion of our patients had higher grades of retinopathy needing surgical intervention. Hence, the findings cannot be translated to the general population.

In conclusion, the co-existence of nephropathy, neuropathy, hypertension, hyperlipidaemia and cardiovascular disease was found in patients with early grades of diabetic retinopathy. These results indicate that a thorough search for concurrent systemic comorbidities must be carried out in all patients with retinopathy irrespective of the severity. This approach may aid in reducing the morbidity and mortality associated with late detection of diabetes end organ damage.

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