

A study of correlation between macular ischaemia and diabetic nephropathy in diabetes mellitus

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Abstract: *Introduction:* Some studies have reported an association between ischaemia of the macula as seen on fundus fluorescein angiography (FFA) with diabetic nephropathy in diabetes mellitus. They have further postulated that finding of macular ischaemia on FFA can be used to predict the onset of diabetic nephropathy in diabetes mellitus. This study was undertaken to explore association between macular ischemia and nephropathy in diabetes mellitus in a rural population of Maharashtra. *Aims and objectives:* To explore for any correlation between ischaemic maculopathy due to diabetes and diabetic nephropathy and to find out whether ischaemic maculopathy can be used as a marker for diabetic retinopathy. *Material and Methods:* Fundus fluorescein angiography was done using 5ml of 20% sodium fluorescein dye to detect macular ischaemia in all the study patients. Serum creatinine, blood urea, and urine examination were done to detect nephropathy. Statistical analysis was done to find out the association between macular ischaemia and diabetic nephropathy. *Observation and Results:* The prevalence of nephropathy was 81% in patients with ischemic maculopathy as compared with 19% in patients without macular ischaemia. This difference was statistically significant with $p < 0.001$. Multivariate analysis revealed that risk factors associated with diabetic nephropathy were presence of macular ischemia (odd ratio 32.9 with $p < 0.001$), age above 65 years (odd ratio 8 with $p < 0.01$), duration of diabetes > 20 years (odd ratio 4.1 with $p < 0.01$), and presence of proliferative diabetic retinopathy (odd ratio 3.2 with $p < 0.01$). *Conclusion:* This study found a strong correlation between ischaemic maculopathy and nephropathy in patients with diabetes mellitus. The association between ischaemic maculopathy and nephropathy remained strong even after adjusting for the confounding factors. The findings of this study suggest that macular ischaemia as seen on FFA can be used to predict the onset of nephropathy in patients with diabetes mellitus and may serve as a potential marker.

Keywords: Diabetic Retinopathy, Diabetic Maculopathy, Diabetic Nephropathy, Macular Ischaemia.

Introduction

The prevalence of diabetes mellitus has increased rapidly in recent decades to assume almost pandemic proportions. The prevalence of diabetes mellitus is expected to rise from 285 million in 2010 to nearly half a billion in 2030 [1]. As the prevalence of diabetes increases, the burden of end-organ diseases such as diabetic retinopathy and diabetic nephropathy also will increase. The prevalence of diabetic retinopathy is around 18% in patients with diabetes mellitus, whereas the prevalence of diabetic retinopathy is around 25% after 10 years of diagnosis of diabetes mellitus in India. Both diabetic retinopathy and nephropathy are due to microangiopathies caused by diabetes. Ischemic maculopathy is an uncommon but

troublesome complication associated with diabetes mellitus [2]. Ischemic maculopathy causes reduction in visual acuity as the macula is critical for central vision [3].

The risk factors and pathogenesis of macular ischemia are not completely understood. Uncontrolled hypertension and poor glycaemic control may increase the risk of ischemic maculopathy as reported by some studies. The risk factors of ischaemic maculopathy might be different from diabetic retinopathy. There is no specific treatment for ischaemic maculopathy except tight glycemic control and treatment of associated systemic hypertension. Anti-VEGF injections and laser

photocoagulation have also been tried in treatment of ischaemic maculopathy. Some studies have reported an association between ischaemia of the macula as seen on fundus fluorescein angiography (FFA) with diabetic nephropathy in diabetes mellitus [4-6].

They have further postulated that finding of macular ischaemia on FFA can be used to predict the onset of diabetic nephropathy in diabetes mellitus. Macular ischaemia may be used as a marker for diabetic nephropathy. This study was undertaken to find out association between macular ischemia and diabetic nephropathy in diabetes mellitus in a rural population of Maharashtra.

Aims and objectives

1. To explore for any correlation between ischaemic maculopathy and diabetic nephropathy and to find out significance of this association.
2. To find out whether ischaemic maculopathy can be used as a marker for diabetic retinopathy

Material and Methods

This cross-sectional study was conducted on 120 patients with diabetes mellitus and diabetic retinopathy coming to ophthalmology outpatient department (OPD) in a medical college in a rural area of Maharashtra. These patients were screened for macular ischaemia by Fundus Fluorescein Angiography (FFA).

Inclusion criteria

- Diabetic patients with diabetic retinopathy ranging from moderate NPDR to PDR.
- Levels of fasting blood sugar (FBS) more than 126mg/dl and levels of post-prandial blood sugar (PPBS) more than 200mg/dl

Inclusion criteria for cases:

- Changes suggestive of ischemia of macula at least in one eye as seen by FFA

Inclusion criteria for controls:

- Absence of macular ischaemia as demonstrated by normal FAZ on FFA

Exclusion criteria:

- Patients not willing to undergo FFA
- Known cases of hypersensitivity to dye
- Medical contra-indications of FFA
- Significant media opacities such as advanced cataract
- Any prior photocoagulation in the macular region - high risk PDR
- Macular ischaemic status doubtful after FFA
- Patients on haemo-/peritoneal dialysis
- PDR with high risk characteristics
- Known cases of diabetic nephropathy

The sample size was calculated using statistical methods taking into account the prevalence of diabetic nephropathy and macular ischaemia in diabetic patients to have enough statistical power to detect difference between two groups.

All the prospective study participants were informed about the study and risks and complications associated with FFA. Patients willing to give informed consent were included in the study. First, a detailed history was taken. Points included in history were duration and control of diabetes and presence/absence of other systemic disorders such as hypertension. Blood pressure was checked in the general examination. Nervous system was examined to detect any signs of diabetic neuropathy.

Visual acuity for distance was recorded with Snellen's chart: Method of finger counting or hand movements was used when the visual acuity was less than 6/60. Perception of light and projection of rays were also recorded. Anterior segment examination was done with a slit lamp with two step magnification to detect findings such as iris neovascularization, presence of corneal nerves, and cataract.

The Goldman applanation tonometer was used to check intraocular pressure (IOP) in all patients. The retina was evaluated for the presence of diabetic retinopathy with an indirect ophthalmoscope and slit lamp biomicroscope with 90 D lens.

Following materials were used for detailed ocular examination and fundus fluorescein angiography.

- Snellen's chart for testing visual acuity
- Slit lamp for detailed anterior segment examination
- Schiottz tonometer to measure intraocular pressure
- Applanation tonometer to measure intraocular pressure
- 0.8% tropicamide plus 5% phenylephrine eye drops for mydriasis to have a better view of the fundus
- Heine ophthalmoscope for direct ophthalmoscopy
- Indirect ophthalmoscope for indirect ophthalmoscopy
- 90 D lens for slit lamp biomicroscopy
- 5 cc syringe for injecting the dye
- 24 gauge needle for injecting the dye
- sodium fluorescein dye for fundus fluorescein angiography (FFA)
- Telecentric FF450 plus fundus camera (VISUPAC system, Carl Zeiss, Germany) for fundus photography and FFA.

Grading of diabetic retinopathy:

The ETDRS severity scale was used to classify diabetic retinopathy as mild, moderate and severe non-proliferative diabetic retinopathy [NPDR]; early and high risk PDR [7]. 5ml of 20% sodium fluorescein dye was used in FFA for detection of ischaemic maculopathy and other changes. During FFA, fovea was targeted to assess the foveal avascular zone (FAZ). Capillary phase of FFA was used for the assessment of FAZ. Blood collection was done and blood was sent for laboratory investigations such as blood sugar levels, serum creatinine and blood urea levels.

Diagnosis of diabetes mellitus:

Following criteria were used for the diagnosis of diabetes mellitus:

- Fasting plasma glucose more than 126 mg/dL
Or
- postprandial plasma glucose more than 200 mg/dL
Or
- Patient already using medication for diabetes.

Definition of diabetes nephropathy:

Following criteria were used to define nephropathy:

- serum creatinine > 1.5 mg/dL
- urine albumin > 30 mg/d (1+ indicative of gross proteinuria) and/or
- blood urea > 40 mg/dL.

Definition of macular ischemia:

Macular ischemia was diagnosed based on criteria described by Bresnick [8]. Moderate FAZ irregularities were considered essential for the diagnosis of macular ischaemia. The irregularities of FAZ were given more importance for the diagnosis of FAZ rather than the size of FAZ. A patient was considered to have macular ischaemia when the diameter of FAZ was more than 1000 μ .

A) Criteria for diagnosis of moderate FAZ irregularities were as follows;

- Dilated and tortuous capillaries encroaching into the FAZ,
- Blood vessels (arterioles or venules) directly abutting margins of FAZ
- Enlarged spaces between capillaries surrounding the FAZ.

B) *Severe FAZ irregularities* were defined as gross enlargement of FAZ with destruction of the structure of FAZ.

C) FAZ was considered normal when the FAZ was less than 1000 in diameter. The other criteria for diagnosis of normal FAZ were regular, round, or oval shape. For the purpose of this study, mild undulations of FAZ were not taken as macular ischaemia and were deemed to be normal [8].

Statistical analysis: Statistical analysis was done to find whether the associations between macular ischemia and diabetic nephropathy were statistically significant. The statistical tests used for this purpose was the student's t-test. Macular ischaemia in the worse eye was considered for the purpose of statistical analysis. Both person-wise analysis and eye-wise analysis were used. The association of various factors with diabetic nephropathy was analysed using multivariate logistic regression analysis. Probability values and odds ratio were calculated with multivariate logistic regression analysis.

Results

Demographic characteristics: 5 out of 120 study participants were cases i.e. they had macular ischaemia and 85 were controls i.e. they had no macular ischaemia. The patients with macular ischemia were significantly older than the

patients without macular ischemia. The mean age was 57.9 in patients with macular ischemia. The mean age was 54.7 in patients without macular ischemia. There was no significant difference in sex distribution in two groups (Table 1).

	Total no of patients N (%)	Patients with macular ischaemia (cases) N (%)	Patients without macular ischaemia (controls) N (%)	p value
	120 (100)	35 (29)	85 (71)	
Male	85 (71)	25 (71)	60 (71)	0.93
Female	35 (29)	10 (29)	25 (29)	
Mean age ± SD	55.7 ± 5.4	57.9 ± 4.8	54.7 ± 5.4	0.003

		Patients with diabetic nephropathy N (%)	Patients without diabetic nephropathy N (%)	p value
All study patients	120 (100)	31 (26)	89 (74)	
Patients with macular ischaemia	35 (29)	25 (81)	10 (11)	<0.001
Patients without macular ischaemia	85 (71)	6 (19)	79 (89)	

Association between macular ischaemia and nephropathy: The prevalence of diabetic nephropathy was 26% in all study patients. The prevalence of diabetic nephropathy was significantly higher (81%) in patients with macular ischaemia as compared with patients without macular ischaemia (11%). This association between diabetic nephropathy and macular ischaemia was found to be statistically significant (p<<0.001). Thus, macular ischaemia emerged as a significant factor associated with diabetic nephropathy in this study (Table 2).

ischaemia as compared to 9.3 years in patients without macular ischaemia. This difference was statistically significant (Table 3).

Blood sugar levels: Patients with macular ischaemia had significantly higher fasting and post prandial blood sugar levels as compared with patients without macular ischaemia. Mean fasting blood sugar levels were 179.8 ± 54.4mg/dL in patients with macular ischaemia as compared with 142.8 ± 51.8mg/dL in patients without macular ischaemia (Table3).

Duration of diabetes: The mean duration of diabetes was 12.3 years in patients with macular

	All subjects	Patients with macular ischaemia (cases)	Patients without macular ischaemia (controls)	p value
Duration of diabetes (years)	10.2 ± 5.5	12.3 ± 5.5	9.3 ± 5.3	0.007
Fasting blood sugar (mg/dL)	153.6 ± 55.0	179.8 ± 54.4	142.8 ± 51.8	<0.001
Post-prandial blood sugar (mg/dL)	226.6 ± 80.0	265.1 ± 89.9	210.7 ± 70.2	<0.001

Table-4: Serum creatinine levels

	Total	Patients with macular ischaemia (cases)	Patients without macular ischaemia (controls)	p value
Serum creatinine(mg/dL)	1.18 ± 0.62	1.52 ± 0.36	1.04 ± 0.65	<0.001

Renal parameters: Patients with macular ischaemia had significantly higher prevalence of impaired renal function and nephropathy as evidenced by serum creatinine levels. Mean serum creatinine levels were 1.52 ± 0.36 mg/dL in patients with macular ischaemia as compared with 1.04 ± 0.65mg/dL in patients without macular ischaemia (Table 4).

Grades of diabetic retinopathy: Presence of proliferative diabetic retinopathy emerged as an important risk factor for macular ischemia. Patients with macular ischaemia were found to have significantly higher prevalence of proliferative diabetic retinopathy (46%) as compared with patients without macular ischaemia (19%) (Table 5).

Table-5: Grade of diabetic retinopathy

	Total N (%)	Patients with macular ischaemia (cases) N (%)	Patients without macular ischaemia (controls) N (%)	p value
Proliferative diabetic retinopathy	32 (27)	16 (46)	16 (19)	0.002
Non-proliferative diabetic retinopathy	88 (73)	19 (54)	69 (81)	

Factors such as age, sex, duration, and presence of proliferative changes were associated with both macular ischaemia and nephropathy as seen in multivariate analysis. After adjusting for these variables also, macular ischaemia retained a strong association with diabetic nephropathy. The odds ratio for risk of prevalence of diabetic nephropathy with macular ischemia was 32.9 with p < 0.001 (Table6).

Duration of diabetes		
≥ 20 years	4.1 (1.0 to 16.6)	0.05
10-19 years	1.6 (0.6 to 3.8)	0.32
0-9 years	Reference	
Fundus findings		
PDR	3.2 (1.4 to 7.8)	0.01
NPDR	Reference	

Table-6: Risk of prevalence (ODDS ratio)

Variables	Odds Ratio (95% Confidence Intervals)	p value
Macular ischaemia		
present	32.9 (10.9 to 99.6)	< 0.001
absent		
Age categories		
> 60 years	8.0 (1.6 to 41.2)	0.01
51-60 years	3.1 (0.7 to 14.9)	0.15
41-50 years	Reference	
Sex		
Male	1.3 (0.5 to 3.2)	
Female	Reference	

Discussion

Ischemic maculopathy and nephropathy due to type 2 diabetes were strongly related with each other in this study. This study also found that other factors associated with diabetic nephropathy were age, duration of diabetes, presence of proliferative changes and high blood sugar levels. Multivariate analysis was done to adjust for the above confounding factors.

Even after adjusting for these factors, there was a strong association between macular ischaemia and diabetic nephropathy. The strength of this study was sample size with enough statistical power. The results of this

study suggest that the presence of macular ischemia on FFA has a strong predictive value for diabetic nephropathy. Macular ischemia may serve as a marker for diabetic nephropathy in future.

There are few studies which have directly studied the correlation between macular ischaemia and diabetic nephropathy. They have reported similar results. Shukla and colleagues did a similar study and found that patients with ischemic maculopathy due to diabetes were more likely to have nephropathy. They also reported a lack of significant association between other systemic diseases and diabetic nephropathy [4]. Bresnick and colleagues also reported that retinal ischemia and impaired renal function were associated. They reported that 75% of patients with macular ischaemia had elevated serum creatinine levels [5].

Das and colleagues also reported that patients with ischemic maculopathy were more likely to have impaired renal functions. They found a strong positive correlation between macular ischaemia and nephropathy [6]. Zander and colleagues did a cross sectional study to examine the association between diabetic maculopathy and other risk factors in diabetic nephropathy. This study reported a close association between diabetic maculopathy and diabetic nephropathy [9].

Severity of diabetic retinopathy was found to be associated with diabetic nephropathy in this study. It might be a potential confounding variable in this study. Studies have reported that the size of FAZ and irregularities of FAZ increased with severity of diabetic retinopathy. In this study also, proliferative diabetic retinopathy was associated with increased prevalence of macular ischaemia. Thus, severity of diabetic retinopathy may be a risk factor for the development of both macular ischaemia and nephropathy [10]. Male gender was a risk factor for development of diabetic nephropathy. The other risk factors associated with development of diabetic retinopathy were male sex and higher glycosylated hemoglobin in this study. Ha and colleagues also reported similar findings [11].

The retinal ischaemia and diabetic nephropathy frequently coexist even without over

manifestations of diabetic retinopathy. Malerbi and colleagues carried out FFA in patients with microalbuminuria in patients with diabetes mellitus without overt diabetic retinopathy at baseline and at follow-up. Even in absence of overt diabetic retinopathy, a significant proportion of patients had microaneurysms, breakdown of the blood-retinal barrier and retinal ischemia in this study [12].

Macular ischemia and nephropathy are due to ischemia because of damage to small blood vessels in macular and kidneys respectively. Both are end organs and damage to small blood vessels in them may occur concurrently. This may explain the concurrent incidence of ischaemic maculopathy and nephropathy. Lee et al in a retrospective study evaluated the clinical records of patients with diabetic retinopathy and nephropathy. They reported that retinal ischaemia manifesting as extensive capillary nonperfusion on FFA increased the risk of diabetic nephropathy [13].

Retinal capillaries and renal glomeruli show basement membrane thickening in diabetes. This may lead to glomerular hyalinisation due to ischemia leading to impaired renal function. A study of retinal vascular signs may be helpful in predicting development of nephropathy in patients with diabetes. Presence of retinal vascular changes at baseline was found to increase the risk of development of diabetic nephropathy over a six year follow-up period in a prospective study carried on two population-based cohorts (Asian and white) in a study [14].

This study was the first of its kind to be done in diabetic population of rural Maharashtra. This study did not have provision for follow up of patients which limited the study of progress of both ischaemic maculopathy and impaired renal function. This was a significant limitation of this study. Prospective studies which include follow-up of patients may shed further light on this subject.

Conclusion

This study found a strong association between ischaemic maculopathy and nephropathy in patients with diabetes mellitus. The other

significant factors associated with diabetic nephropathy in this study were age, sex, duration, and severity of retinopathy. The association between ischaemic maculopathy and nephropathy

remained strong even after adjusting for the above factors. Ischemic maculopathy as seen on FFA may have a role in predicting the onset of diabetic nephropathy.

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