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## Prevalence of retinopathy in non insulin dependent diabetes mellitus at a diabetes centre in Southern India

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### Abstract

A cohort of 6792 NIDDM patients attending a diabetes centre at Madras in South India was screened using a combination of retinal photography and clinical examination by retinal specialists. A total of 2319 patients (34.1%) had evidence of retinopathy. This included 2090 patients (30.8%) with non-proliferative diabetic retinopathy including 435 patients (6.4%) with maculopathy and 229 patients (3.4%) with proliferative diabetic retinopathy. Multiple logistic regression analyses showed that duration of diabetes, glycosylated haemoglobin, type of treatment (insulin treatment versus non-insulin treatment), systolic and diastolic blood pressures and serum creatinine, showed a positive association with retinopathy while body mass index (BMI) showed an inverse association. The prevalence rates of retinopathy in Southern Indians are comparable to those seen in Europeans. However in view of the high prevalence of diabetes in the Indian sub-continent, diabetic retinopathy could become a formidable challenge in the future.

**Keywords:** Diabetic retinopathy; NIDDM; South India; Risk factors

### 1. Introduction

The prevalence of non-insulin dependent diabetes mellitus (NIDDM) is known to be very high among migrant Asian Indians [1,2] as well as within the Indian sub-continent [3,4]. NIDDM

in India differs from that seen among Europeans in several aspects [5]: (1) the onset of diabetes occurs at a younger age [6], (2) obesity is less common [4] and (3) genetic factors appear to be stronger [7,8]. Studies of vascular complications in Indian NIDDM are therefore of great interest. There is very little data on the prevalence of diabetic retinopathy from India. This paper reports on the prevalence of retinopathy in

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NIDDM patients at a diabetes centre in Southern India.

## 2. Patients and methods

The MV Diabetes Specialities Centre (MVDSC) is a large centre for diabetes at Madras in Southern India. A total of 8449 NIDDM patients were registered at the MVDSC., during a period of one and a half years. During the same period 122 patients with Insulin Dependent Diabetes Mellitus (IDDM) and 62 patients with Fibrocalculous Pancreatic Diabetes (FCPD) were also registered at this centre. Retinopathy in IDDM and FCPD at our centre have been reported in earlier publications [9,10]. Hence this paper only deals with retinopathy in NIDDM. Of the NIDDM patients, 6792 patients (80.4%) could undergo eye tests and they formed the study cohort. The remaining 1657 patients (19.6%) could not be tested for various reasons such as inability to undergo dilatation of eyes because they were driving a vehicle, infections in the eye and dense cataracts. In some cases the diagnosis of diabetes was not yet established at the time of registration at the centre, but was only proved later after the investigations and some patients simply refused to undergo an eye test. There were no significant differences in the age or sex distribution, the duration of diabetes or glycaemic control in these 1657 patients compared to the 6792 patients' who underwent the eye examination.

All study patients underwent a detailed ocular examination which included assessment of visual acuity using a standard Snellen's chart with internal illumination. The best visual acuity obtained with the patients' own glasses and/or pin-hole was recorded. Biomicroscopy of the anterior segment was done to document any abnormalities and the intra ocular pressure was done using a Shiotz tonometer.

## 3. Retinal examination and photography

One drop each of phenylephrine 10% and tropicamide 1% was then instilled into both eyes and

the drops were repeated till the best possible mydriasis was obtained. When the dilatation of the pupils was not satisfactory even after repeated instillation of these drops, homatropine or atropine drops were applied with caution after ruling out cardiovascular problems. For retinal assessment both direct and indirect ophthalmoscopy was done by two retinal specialists. The first (MR) had previously been trained in retinal diseases in the UK and had participated in a study involving clinical grading of retinal lesions [11]. Agreement between the two observers was estimated using the formula:

$$\kappa = \frac{\text{Crude agreement} - \text{Chance agreement}}{1 - \text{Chance agreement}}$$

A value of  $\kappa$  between 0.81 and 1.00 is regarded as very good agreement. In this paper a  $\kappa$  value was 0.95 indicating that the interobserver variation was less than 5%. This degree of agreement could be achieved because both specialists had worked together for over eight years and participated in similar studies earlier.

Due to limited resources and the large numbers studied, retinal photography was done only in patients with any degree of retinopathy. Retinal photography could be performed in 2120 of the 2319 patients with retinopathy while in the remaining 199 patients it could not be done due to various reasons. 45° photographs were taken using a Topcon VT-50 camera of three fields in both eyes. The three photographic fields selected were: (1) one stereo pair of the posterior pole centered on the fovea to show the macula and optic disc (2) one temporal field whose nasal edge touched the macula and (3) the third field was centered as far as possible nasally to the optic disc with the disc on the edge of the field. The photographs were graded singly by MR using the Hammer-smith Hospital grading system [12]. The photographs were assessed both for the presence and severity of retinopathy, and for photographic quality. Photographic quality was assessed on an arbitrary scale from 1 to 5, 1 being excellent, 2 good and easily accessible, 3 assessable with some difficulty, 4 only part of the field assessable and 5 being unassessable. In 190 (9%) of the patients, photographs were not assessable.

There was concurrence between the ophthalmological and photographic assessments of the presence or absence of retinopathy in 1717 of 2120 patients (80.9%). Of the remaining 403 cases, the majority (394) had minimal lesions eg. few microaneurysms which were missed by the clinical examination, while the remaining nine cases had more severe degrees of retinopathy including two cases with proliferative retinopathy.

The minimal criteria for diagnosis of diabetic retinopathy was the presence of at least two microaneurysms in any field. Retinopathy, when present, was classified as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR was further subdivided into NPDR with and without maculopathy based on the presence or absence of maculopathy. Maculopathy was defined as the presence of retinal thickening and or exudates within 500  $\mu\text{m}$  of the fovea. Proliferative diabetic retinopathy (PDR) was defined as the presence of abnormal new vessels on the disc (NVD) or elsewhere (NVE). Advanced diabetic eye disease comprised of patients with fibrous retinitis proliferans, vitreous haemorrhage and traction detachment of the retina. In the event of the two eyes showing different grades of retinopathy, the worse eye was included as the final grade of DR. Patients who had both PDR and maculopathy were graded as PDR.

The height and weight were recorded and the body mass index (BMI) was calculated using the formula: weight (kg) divided by height ( $\text{m}^2$ ). All biochemical studies were done at the time of the first visit to the centre using a random access autoanalyser (Corning Express Plus USA). Fasting and post prandial (after a standard breakfast) plasma glucose estimations were done by the glucose oxidase method, serum cholesterol by the CHOD-PAP method, serum triglycerides by the GPO-PAP method and serum creatinine by the modified kinetic method of Jaffe using kits supplied by Boehringer Mannheim, Germany. Glycosylated haemoglobin (HbA1c) was done using high pressure liquid chromatography (HPLC) by the Variant Machine (Bio Rad, USA).

#### 4. Statistical analyses

Analyses were performed using SPSS program (Version 4.0.1.) on an IBM PC compatible computer. Student's *t*-test was used for comparison of group means. Log transformation was done to stabilize the variance wherever indicated. Multiple logistic regression analysis was done to look for the risk factors associated with diabetic retinopathy. The method of regression was backward deletion method. Variables were included on the basis of univariate analysis and previous studies. The dependent variable was 'any diabetic retinopathy' versus 'no diabetic retinopathy' and independent variables were age, duration of diabetes, body mass index, systolic and diastolic blood pressure, smoking, HbA1c, fasting and postprandial plasma glucose, cholesterol, triglycerides, serum creatinine, family history of diabetes mellitus and type of treatment (i.e insulin versus non-insulin treatment). Continuous variables were categorized appropriately.

#### 5. Results

A total of 1062 patients (15.6%) had impaired vision (visual acuity  $< 6/9$ ) and 11 patients (0.2%) were registered legally blind (visual acuity  $< 6/60$  in both eyes). In 472 patients (44.5%) the decreased visual acuity was due to diabetic retinopathy related causes. In the remaining cases the major cause of decreased visual acuity was cataract. Maculopathy accounted for 78.8% of the decrease in visual acuity among the diabetes related causes while the remainder comprised of vitreous haemorrhage and advanced diabetic eye disease. Table 1 shows the prevalence of retinopathy. A total of 2319 patients (34.1%) had retinopathy. This comprised of 2090 patients (30.8%) with non-proliferative diabetic retinopathy (NPDR) which included maculopathy in 435 patients (6.4%) and 229 patients (3.4%) with proliferative diabetic retinopathy (PDR).

Fig. 1 shows the break-down of the retinopathy according to the duration of diabetes. At the time of diagnosis of diabetes, 7.2% had

Table 1  
Prevalence and type of retinopathy ( $n = 6792$ )

	Total	Male	Female
<b>Non proliferative diabetic retinopathy (NPDR)</b>			
(a) Without maculopathy	1655	1092	563
(b) With maculopathy	435	267	168
<b>Total NPDR</b>	<b>2090</b>	<b>1359</b>	<b>731</b>
	(30.8%)		
<b>Proliferative diabetic retinopathy (PDR)</b>			
New vessels (NVD and NVE)	138	79	59
Advanced Diabetic Eye Disease	91	62	29
<b>Total PDR</b>	<b>229</b>	<b>141</b>	<b>88</b>
	(3.4%)		
<b>Total Diabetic Retinopathy</b>	<b>2319</b>		
	(34.1%)		

NVD New Vessels on Disc.

NVE New Vessels elsewhere.

NPDR and 0.2% PDR. There was a steady increase in the prevalence of both NPDR and PDR with increasing duration of diabetes. After 20 years duration of diabetes, the prevalence of NPDR tended to plateau off at about 73% while that of PDR reached a figure of 11.9%.

Fig. 2 shows the breakdown of the maculopathy in relation to the duration of diabetes. There

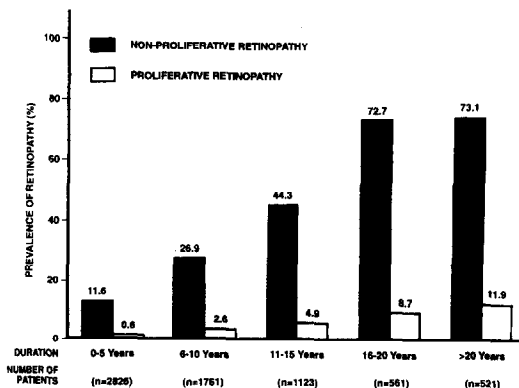


Fig. 1. The prevalence of retinopathy (non-proliferative and proliferative) in relation to the duration of diabetes.

was an increase in prevalence of maculopathy from 1.2% between 0 and 5 years to 14.1% between 11 and 15 years. Thereafter there was a decline, but this may be related to an increase in PDR as those with PDR plus maculopathy were classified under PDR.

Table 2 shows the clinical and biochemical details of the patients with NPDR and PDR compared to those with no retinopathy. The duration of diabetes was greater in those with NPDR and

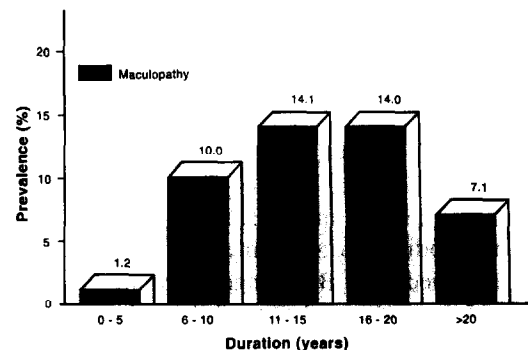


Fig. 2. The prevalence of maculopathy in relation to the duration of retinopathy.

Table 2  
Clinical and biochemical factors in diabetic retinopathy

Variable	Study group			Significance ( <i>P</i> values)		
	No DR ( <i>n</i> = 4473)	NPDR ( <i>n</i> = 2090)	PDR ( <i>n</i> = 229)	NPDR vs No DR	PDR vs No DR	NPDR vs PDR
Age of the patient (years)	54.4 ± 10.1	56.2 ± 9.5	57.0 ± 9.8	NS	NS	NS
Duration (years)	6.6 ± 5.7	12.5 ± 7.4	15.0 ± 7.1	<0.001	<0.001	<0.001
Systolic BP (mm Hg)	132 ± 17	136 ± 19	145 ± 23	<0.001	<0.001	<0.001
Diastolic BP (mm Hg)	84 ± 8	84 ± 8	87 ± 10	NS	<0.001	<0.001
BMI (kg/m <sup>2</sup> )	25.3 ± 4.0	24.3 ± 3.7	23.5 ± 3.7	<0.001	<0.001	0.003
FPG (mmol/l)	9.2 ± 3.0	10.6 ± 3.5	10.6 ± 3.8	<0.001	<0.001	NS
PPPG (mmol/l)	14.1 ± 4.0	15.7 ± 4.2	15.7 ± 4.7	<0.001	<0.001	NS
HbA1c (%)	10.0 ± 1.3	10.3 ± 1.3	10.3 ± 1.3	<0.001	<0.001	NS
Cholesterol (mmol/l)	5.3 ± 0.9	5.4 ± 1.1	5.5 ± 1.4	NS	0.001	NS
Triglyceride (mmol)	2.1 ± 1.3	2.1 ± 1.5	2.2 ± 1.7	NS	NS	NS
Creatinine (μmol/l)	61.9 ± 8.8	70.7 ± 26.5	88.4 ± 61.9	<0.001	<0.001	<0.001

DR Diabetic retinopathy.

NPDR Non-proliferative diabetic retinopathy.

PDR Proliferative diabetic retinopathy.

FPG Fasting plasma glucose.

PPPG Post-prandial plasma glucose.

HbA1c Glycosylated haemoglobin.

All numbers are Mean ± Standard Deviation.

PDR, compared to those without diabetic retinopathy ( $P < 0.001$ ). The systolic blood pressure was significantly higher in the retinopathy groups. The diastolic blood pressure was significantly higher in the PDR group compared to NPDR and no DR groups ( $P < 0.001$ ).

Both fasting and post-prandial plasma glucose levels were significantly higher in the NPDR and PDR patients compared to those without diabetic retinopathy ( $P < 0.001$ ). Glycosylated haemoglobin (HbA1c) levels were significantly higher in patients with NPDR and PDR compared to those without diabetic retinopathy ( $P < 0.001$ ).

The serum cholesterol was significantly higher in the PDR group compared to the group without retinopathy ( $P = 0.001$ ) but differences between other groups were not statistically significant. Serum creatinine levels were significantly higher in the NPDR and still higher in the PDR group ( $P < 0.001$  between all groups).

Table 3 gives the results of the multiple logistic regression analysis. Only variables which had a

significant association with retinopathy are listed in the table. Duration of diabetes, glycosylated haemoglobin, type of treatment (insulin treatment versus non-insulin treatment), systolic and diastolic blood pressures and serum creatinine showed a positive association with retinopathy while BMI showed an inverse association with retinopathy. There was also an inverse relationship between HbA1c and falling BMI on univariate regression analysis and the regression equation was  $HbA1c = 10.69 - BMI(0.2224)$ ,  $P < 0.001$ .

## 6. Discussion

This paper presents the prevalence of retinopathy in a cohort of south Indian NIDDM patients attending a diabetes centre who were screened for retinopathy irrespective of presence of visual symptoms or the duration of diabetes. It must be pointed out that ours is a private diabetes centre where the majority of patients pay for the services. The socio-economic status of this study

Table 3  
Logistic regression analysis for factors associated with retinopathy

Variable	Regression co-efficient (b)	SE (b)	P value	Odds ratio (95% CI)
Duration of DM	0.48	0.03	<0.0001	1.62 (1.53,1.72)
Glycosylated haemoglobin (%)	0.32	0.06	<0.0001	1.38 (1.22,1.55)
Type of treatment (insulin vs non-insulin treated)	1.44	0.08	<0.0001	4.24 (3.63,4.95)
Body Mass Index	0.09	0.03	0.0004	0.92 (0.87,0.96)
Systolic BP	0.19	0.05	0.0004	1.20 (1.09,1.33)
Diastolic BP	0.31	0.14	0.03	1.36 (1.02,1.80)
Serum creatinine	0.09	0.03	0.003	1.09 (1.03,1.16)

SE Standard error.

CI Confidence interval.

Categories used for continuous variables:

Duration 5 year intervals.

Blood pressure 25 mm/Hg.

Serum creatinine 0.5 mg/dl (44  $\mu$ mol/l).

Glycosylated haemoglobin 1%.

cohort could therefore be different from the general population. It is also possible that some patients come to the centre specifically because of the availability of retinal services but this was estimated to be less than 10% of all patients attending our centre. These factors might introduce a referral bias and thus influence the prevalence rates observed in this paper. Finally, due to financial and logistic reasons we could not photograph the eyes of all patients, particularly those with no evidence of retinopathy. It is possible that this could also influence the prevalence rates observed in the study. However the large number of patients studied and the absence of any data on retinopathy from the Indian sub-continent still makes the study valuable.

The overall prevalence of retinopathy was 34.1% of which 30.8% was NPDR and 3.4% PDR. Comparison of retinopathy rates across different countries is difficult because of differences in type of diabetes (NIDDM or IDDM), number of patients studied and the different methods used for screening of the patients [13]. Caird et al. [14] found a 36.8% prevalence rate of NPDR in a survey which involved 4076 diabetic patients with over 10 years duration of diabetes. Dorf et al. [15] reported a 3% prevalence rate of NPDR at the time of diagnosis of diabetes. In our study, the prevalence of NPDR and PDR were 7.2% and 0.2% at the onset of diabetes and 73%

and 11.9% after 20 years duration of diabetes. These figures are lower than those reported by other workers [16–21]. In most 'western' studies the prevalence of retinopathy at diagnosis varies from 20 to 30%. The reason for these differences are not clear. Klein et al [20] using retinal photography reported that 23% of their patients had retinopathy at less than 2 years duration of diabetes. It is possible that the lower prevalence rates of retinopathy in this paper is related to the lower sensitivity of clinical examination which was done in our study compared to retinal photography which was done in many other studies. However it is of an interest that a recent paper from Madras reported that 6.7% of newly diagnosed NIDDM had retinopathy using clinical criteria, a figure similar to that reported in this paper [22].

Proliferative retinopathy is reported to be less common in NIDDM than in IDDM [19,20]. 40% of NIDDM patients who develop PDR do so within 10 years duration of diabetes [16–20]. A recent study from Finland [23] reported a prevalence of 37% for NPDR and 8% for PDR in long term NIDDM patients. Another study in Polynesians of Western Samoa [24] reported a prevalence rate of 43.2% for NPDR and 4.5% for PDR.

The best epidemiological data on retinopathy to date is the Wisconsin data by Klein et al. [19,20]. Using retinal photography, Klein et al. [19] showed that in those diabetic patients above 30

years and not receiving insulin, 70% had some form of retinopathy after 20 years duration while PDR was seen in 10–15% of patients. The group receiving insulin had higher prevalence rates of both NPDR and PDR.

The overall prevalence of maculopathy was 6.4% in this series and this showed a relationship with duration and in those with 11–20 years duration of diabetes about 14% of patients had maculopathy. After 20 years there was a decrease in maculopathy which is probably due to the fact that the prevalence of PDR increased significantly after this period and the cases with both PDR and maculopathy were classified as PDR. Maculopathy was also found to contribute to 78.8% of the decrease in the visual acuity of the diabetic retinopathy related causes while cataract contributed to the majority of non retinopathy related causes of decreased visual acuity in this series.

The results of our logistic regression analysis show that duration of diabetes, glycosylated haemoglobin, type of treatment (insulin vs non insulin treatment), systolic and diastolic blood pressure and serum creatinine levels show a positive association with retinopathy. This study thus confirms that the two most important risk factors for retinopathy in Europeans are also present in Indians, namely duration of diabetes and control of diabetes. The correlation with duration of diabetes is well known [16–21]. The role of hyperglycaemia in the development of diabetic retinopathy is also well known and has been elegantly demonstrated in the Diabetes Control and Complications Trial [25]. In this paper a strong association is also seen between HbA1c and retinopathy. The lack of correlation with fasting and postprandial plasma glucose levels is probably related to the fact that a number of patients with retinopathy were recently changed over to insulin therapy because of sub-optimal control. This is further confirmed by the strong correlation between the type of treatment i.e. insulin treatment and retinopathy. Although the link with blood pressure has been suggested [26] a causal relationship has not been identified. Hypertension can occur either before or after the development of retinopathy. It is however not clear whether the hyperten-

sion factor in retinopathy is linked to the presence of nephropathy or renal insufficiency as shown by the association of retinopathy with serum creatinine levels in this paper. Indeed the relationship between nephropathy and retinopathy particularly with respect to its timing and development remain unclear [27,28]. The inverse relationship between BMI and retinopathy is probably related to the higher HbA1c values as there was an association between HbA1c and falling BMI.

In summary, we present data on the prevalence of retinopathy in a large cohort of South Indian NIDDM patients attending a diabetes centre at Madras. Although the prevalence rates of retinopathy in South Indian NIDDM patients is similar to that seen in Europeans, given the high prevalence rate of diabetes in the Indian sub-continent, diabetic retinopathy could pose a formidable challenge in the future.

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