

Natural History of Retinopathy in FCPD, MODY and IDDM - A Follow-Up Study

M. Rema, V. Mohan, M. Ponnaiya

ABSTRACT

This paper reports for the first time on the natural history of diabetic retinopathy in three forms of youth onset diabetes seen in our country based on a 4 year follow-up study. Forty patients each with Fibrocalculous Pancreatic Diabetes (FCPD), Maturity Onset Diabetes of Youth (MODY) and Insulin-Dependent Diabetes Mellitus (IDDM) were followed for periods up to four years with annual fundus colour photography using an international retinal grading system. All patients had early background diabetic retinopathy at the onset of the study. The rate of progression of retinopathy was found to be similar in all three study groups. The study proves that patients with secondary forms, of diabetes (FCPD) also develop retinopathy at the same rate as primary forms of diabetes. Moreover, it disproves earlier studies that patients with MODY are protected from retinopathy.

Diabetic retinopathy is the leading cause of blindness in all developed countries [1]. There is very little data on diabetic retinopathy from developing countries. In South India, there are some unique forms of diabetes that are extremely rare in Western countries. Fibrocalculous Pancreatic Diabetes (FCPD) is a type of diabetes that is secondary to Tropical Calcific Pancreatitis (TCP) [2]. The highest known prevalence of FCPD in the world is in Southern India [3]. Maturity Onset Diabetes of Youth (MODY) is a form of Non-Insulin-Dependent Diabetes Mellitus characterized by autosomal dominant inheritance and onset in youth. We [4] and others [5] have shown that MODY is highly prevalent among Indians.

It was earlier believed that retinopathy was rare in FCPD [2] and in MODY subjects [6]. We have documented in earlier studies that retinopathy does occur in FCPD [7] and in MODY patients [4]. However both these studies were cross-sectional in nature and there is virtually no longitudinal studies on the natural history of diabetic retinopathy in our country.

In this study we present a four year follow-up study of diabetic retinopathy in FCPD and MODY patients and compare the results with a group of Insulin-Dependent Diabetes Mellitus (IDDM) patients. Our aim was to study patients of similar age group, namely FCPD, MODY and IDDM, all of which present at a younger age. For this reason, classical NIDDM which usually develops at a later age, was not included in this study.

PATIENTS AND METHODS

The criteria for diagnosis of diabetes was based on WHO Study Group criteria [8]. The criteria for diagnosis of FCPD, MODY and IDDM are given below:

FCPD

Diabetic patients classified under this group gave usually a history of recurrent abdominal pain from childhood and had unequivocal evidence of pancreatic calculi on a plain abdominal roentgenogram and/or other features of chronic pancreatitis according to the criteria of Mohan [9]. In every patient other causes of chronic pancreatitis (eg. alcoholism) were excluded.

MODY The criteria of Tattersal and Fajans [10] were used for diagnosis of MODY namely:

- Age at diagnosis of diabetes less than 25 years.
- Control of fasting hyperglycaemia for a minimum period of 2 years without insulin.
- Absence of ketosis at any time.
- Autosomal dominant inheritance.

IDDM Patients classified under this group had abrupt onset of symptoms, were prone to ketosis in the basal state, had evidence of ketoacidosis in the past and were consistently on insulin therapy, either from the time of diagnosis or shortly thereafter. Additionally, all patients had fasting plasma C-peptide < 0.1 pmol/ml and stimulated levels < 0.2 pmol/ml.

Inclusion Criteria

Only patients who had minimal background diabetic retinopathy (with few scattered microaneurysms) corresponding to level 21 of the internationally accepted Early Treatment Diabetes Retinopathy Study (ETDRS) adaptation of the Wisconsin grading system of retinopathy [11] were included in the study. Patients with nephropathy, cardiac disease, hypertension or systemic diseases were excluded from the study.

Clinical and Biochemical Studies

Baseline studies included a complete physical examination including height, weight and body mass

index. Fasting and post-prandial plasma glucose estimations by glucose oxidase method, serum cholesterol by CHOD-PAP method and triglycerides by GOP-PAP method, blood urea by modified Berthelot method and serum creatinine by modified kinetic method of Jaffe were done in all patients using Corning Express Plus Autoanalyser (Corning, USA). Plain roentgenogram of chest and abdomen, ECG and doppler studies were also done in all cases.

Ophthalmic Studies

At baseline, all patients underwent a complete ophthalmic examination including visual acuity testing (with pin hole), slit lamp, anterior segment examination and ocular pressure studies. A detailed retinal examination was done using direct and indirect ophthalmoscopy. A seven field stereoscopic colour photography was done in all cases and the retinopathy was graded using the ETDRS adaptation of the Wisconsin grading system [11]. The grading was done in a 'blinded' manner so that the grader was unaware of whose photograph was being graded. Grading was done by an ophthalmologist (M. Rema) who had experience in grading previous international studies.

ETDRS Classification of Retinopathy

Level 10 : No retinopathy

Level 21-31 : Minimal to mild non-proliferative retinopathy

Level 41-51 : Moderate to severe non-proliferative retinopathy

Level 60 : Fibrous proliferations only

Level 65 : Early proliferative changes

Level 70-80 : Proliferative retinopathy with Diabetic Retinopathy Study high risk characteristics for severe visual loss or the most severe retinopathy leading to ungradable eyes because of vitreous haemorrhage or other complications of diabetic retinopathy.

Retinopathy levels for each individual was derived by giving the eye with the higher level (more severe retinopathy) greater weight. 'Progression' of retinopathy was considered to have occurred if the retinopathy showed a worsening by atleast 2 levels.

Follow-up

Patients were seen annually and all clinical and biochemical tests were repeated at yearly intervals. Retinal colour photography was done in all cases on an annual basis and the retinopathy was graded again. The period of follow-up was upto 4 years.

RESULTS

Table 1 outlines the clinical characteristics of the three study groups at the onset of the study (baseline). It can be seen that there were no significant

differences in age, sex, duration of diabetes or blood pressure between groups. The mean body mass index was lower in the FCPD and IDDM groups compared to the MODY group.

Table 1
Clinical Characteristics of Study Groups at Baseline (Onset of Study)

Parameter	FCPD n = 40	MODY n = 40	IDDM n = 40	P Value Significance		
				FCPD vs MODY	FCPD vs MODY	IDDM vs MODY
Sex Ratio M:F	25:15	24:16	22:18			
Age (Yrs)	40±19	39±7	38±12	NS	NS	NS
Duration of Diabetes (Yrs)	13±5	15±6	14±6	NS	NS	NS
Body Mass Index (BMI) (kg/m ²)	19.3±2.4	24.2±3.4	2.3±2.9	P<0.001	P=0.003	P<0.001
Systolic BP (mm Hg)	125±17	125±21	117±17	NS	NS	NS
Diastolic BP (mm Hg)	81±2	80±1	75±9	NS	NS	NS

FCPD - Fibro-calculeous Pancreatic Diabetes

MODY - Maturity Onset Diabetes of Youth

IDDM - Insulin-Dependent Diabetes Mellitus

NS - Not Significant

Table 2 details the baseline biochemical characteristics between the three groups (P < 0.001). There was no significant difference in the fasting or post-prandial plasma glucose, glycosylated haemoglobin or triglyceride levels between the three groups. The serum cholesterol levels were lower in the FCPD group compared to other two groups (P < 0.001 vs MODY, P < 0.003 vs IDDM).

Table 2
Biochemical Characteristics of Study Groups (at baseline)

Parameter	FCPD n = 40	MODY n = 40	IDDM n = 40	Significance		
				FCPD vs MODY	FCPD vs MODY	IDDM vs MODY
Fasting Plasma Glucose (mg/dl)	207±76	223±79	206±93	NS	NS	NS
Glycosylated Haemoglobin (%)	10.7±1.6	10.4±1.2	10.4±1.5	NS	NS	NS
Serum Creatinine	0.8±0.3	0.7±0.1	0.7±0.2	NS	NS	NS
Seum Cholesterol (mg/dl)	182±30	217±30	214±48	P<0.001	P=0.002	NS
Serum Tryglycerides (mg/dl)	126±98	126±86	130±81	NS	NS	NS

Table 3 shows the follow-up biochemical parameters at the end of the study. There is no significant difference between the three groups with respect to fasting plasma glucose levels or glycosylated haemoglobin levels. However, in all three groups the fasting plasma glucose and glycosylated haemoglobin levels showed significant improvement during the study and the mean value decreased from 10.5% to 9%.

Table 3
Biochemical Parameters at End of Study
in Three Groups

Parameter	FCPD n = 40	MODY n = 40	IDDM n = 40	Significance		
				FCPD vs MODY	FCPD vs MODY	IDDM vs MODY
Fasting plasma Glucose(mg/dl)	156±49	140±40	166±50	NS	NS	NS
Glycosylated Haemoglobin	9.5±2.0	9.1±1.8	9.8±2.0	NS	NS	NS

Table 4 shows the results of the progression of diabetic retinopathy in the three groups. Follow-up data was available in 32 FCPD, 23 MODY and 34 IDDM patients. The results showed that 21/32 FCPD patients (65.5%), 14/23 MODY patients (60.8%) and 21/34 IDDM patients (61.7%) showed progression of the diabetic retinopathy. Figure 1 shows the results in a graphical form.

Table 4
Progression of Diabetic Retinopathy
in the Three Groups

	Progression of Retinopathy	
	With Progression	No Progression
FCPD n = 32	21 (65.6%)	11 (34.4%)
MODY n = 23	14 (60.8%)	9 (39.2%)
IDDM n = 34	21 (61.7%)	13 (38.3%)

Chi Square test = 0.6, N.S.

FCPD - Fibro-calculeous Pancreatic Diabetes

MODY - Maturity Onset Diabetes of Youth

IDDM - Insulin-Dependent Diabetes Mellitus

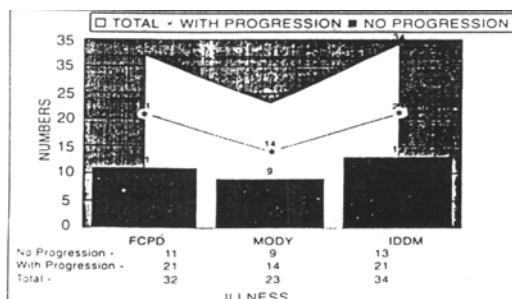


Fig 1: Progression of Diabetic Retinopathy in FCPD, MODY and IDDM patients.

Table 5 shows the mean period of follow-up in the three groups studied. There was no significant difference in the period of follow-up between those with and without progression of the retinopathy.

Table 5
Mean Duration of Follow-up .(Years)

Forms	Groups with Progression	Groups without Progression	P-Value
FCPD	2.9±0.9	2.6±0.2	NS
MODY	2.8±1.5	2.3±1.1	NS
IDDM	2.5±0.7	2.1±0.8	NS

FCPD - Fibro-calculeous Pancreatic Diabetes
MODY - Maturity Onset Diabetes of Youth
IDDM - Insulin-Dependent Diabetes Mellitus
NS - Not Significant

DISCUSSION

The study provides data for the first time on the natural history of diabetic retinopathy in three groups of young diabetics seen in South India namely FCPD, MODY and IDDM. There is virtually no data in existing literature on the natural history of retinopathy in FCPD and MODY as both entities are rare in European populations.

Earlier studies had suggested that being a secondary form of diabetes, FCPD patients do not develop diabetic retinopathy. This was stated in Geevarghese's earlier monogram on Pancreatic Diabetes published in 1968 [2]. In 1985, in his second monogram [3], Geevarghese revised his view and stated that retinopathy does occur in FCPD. It is noteworthy that he had a chapter on retinopathy in this volume. This change in view point was obviously based on the longer follow-up of his patients. In our study published in 1985 [7] we showed for the first time that not only do FCPD patients develop retinopathy but that they also develop sight threatening forms of the disease.

There is no longitudinal follow-up data on the natural history of diabetic retinopathy in FCPD as both Geevarghese's [3] as well as our earlier study [7] were cross sectional in nature. In this unique followup study using internationally accepted methodology we provide evidence that progression of retinopathy does occur in FCPD patients and that the rate of progression is the same as in the two other groups of diabetics, namely MODY and IDDM. Thus patients with FCPD, a secondary form of diabetes, appear to be as prone to microvascular complications of diabetics, as those with primary forms of diabetes.

The data on MODY is also of great interest. The occurrence of retinopathy in MODY is still an unsettled issue. While Tattersal [5] maintains that retinopathy does not occur in MODY, Fajans [12] has shown that it does occur. Our present study supports the latter's view that subjects with MODY not only develop retinopathy but also have a rate of progression that is similar to IDDM patients.

We are unable to find any specific reasons for progression or lack of progression of retinopathy from our study. It is clear that the control of diabetes was not optimum in any of our patient groups although there was a decrease in the mean glycosylated haemoglobin at the end of the study. This could explain the reason why over 60% of patients in all three groups showed some degree of progression. However there were no significant differences between this 60% and the 40% who did not progress, either in the clinical or biochemical parameters.

This raises the question of a genetic susceptibility to retinopathy. In a recent study, we showed that there is a genetic susceptibility to the development of proliferative diabetic retinopathy [13]. It is likely that this is not a chance finding, because study numbers were large and moreover another study from the UK [14] had also shown similar findings. If these findings are confirmed by our presently ongoing studies, it will help to explain the paradox often seen in clinical practice of some patients with good control developing retinopathy and others with poor control who never develop retinopathy.

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