

Autonomic Dysfunction in Non-insulin-dependent Diabetes Mellitus and Fibrocalculous Pancreatic Diabetes in South India

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The prevalence of cardiovascular autonomic dysfunction in non-insulin-dependent (Type 2) diabetes mellitus (NIDDM) and fibrocalculous pancreatic diabetes (FCPD) was assessed by a standard battery of autonomic dysfunction tests involving heart rate responses and blood pressure responses. Three hundred and thirty-six patients with NIDDM and 40 patients with FCPD were studied. Logistic regression analysis was done to look for risk factors associated with autonomic dysfunction. Abnormalities of autonomic function tests were detected in 120 NIDDM patients (35.7%) and 9 FCPD patients (22.5%). There was no significant difference in severity of autonomic dysfunction between NIDDM and FCPD groups. There was an increase in prevalence of autonomic dysfunction with age and duration of diabetes both in NIDDM and FCPD. In the 0–5 years duration group, 28.2% of NIDDM and 16.6% of FCPD had evidence of disordered autonomic function and these figures increased to 56.2% and 60% respectively, after 16–20 years duration of diabetes. Logistic regression analysis showed that only peripheral dysfunction was associated with autonomic dysfunction in NIDDM patients ($r = 0.66$, $p = 0.02$).

KEY WORDS Fibrocalculous pancreatic diabetes Non-insulin-dependent diabetes mellitus Autonomic dysfunction

Introduction

Autonomic dysfunction is a well-recognized complication of diabetes mellitus, particularly in those with long duration of diabetes and in association with peripheral dysfunction.^{1,2} Most earlier studies have reported on autonomic dysfunction in insulin dependent (Type 1) diabetes mellitus (IDDM)^{3–7} and there are relatively few studies in non-insulin-dependent (Type 2) (NIDDM) patients.^{8,9}

NIDDM in Asian Indians has several interesting features. The prevalence is high,¹⁰ genetic (hereditary) factors appear to be strong,^{11,12} obesity is less common¹⁰ and the onset of diabetes is at a young age.^{13,14} There are very few studies on autonomic dysfunction in NIDDM patients from the Indian subcontinent and these have been based on very small numbers.^{15–17} In addition, diabetes in India may be associated with fibrocalculous pancreatic diabetes (FCPD), a term introduced by the WHO study group report on diabetes to describe a unique form of diabetes secondary to tropical chronic pancreatitis. Patients with FCPD are usually young, lean,

poor and have large intraductal pancreatic calculi with marked ductal dilatation.^{1,18} The subject of FCPD has been extensively reviewed.^{18–23} Until recently diabetes related complications were believed to be rare in FCPD.²⁴ However our earlier work showed that retinopathy,²⁵ nephropathy,²⁶ peripheral dysfunction²⁷ and left ventricular dysfunction²⁸ are common, in FCPD, although macrovascular disease occurs less frequently.^{26,29} Only one study has looked at autonomic dysfunction in fibrocalculous pancreatic diabetes (FCPD) but this was done on small numbers and no comparison with NIDDM was made.³⁰

In this study we report on the prevalence of autonomic dysfunction in NIDDM and FCPD patients seen at a diabetes centre in Southern India.

Patients and Methods

The study group comprised 336 patients with NIDDM and 40 patients with FCPD attending the M.V. Diabetes Specialities Centre, a large referral centre for patients with diabetes in southern India. NIDDM comprises 95% and FCPD 1% of all patients seen at the centre.³¹ For NIDDM, every fifth patient registered at the centre over a 4-month period was selected for the study. For FCPD, 40 consecutive patients were included in the study. Patients who were acutely ill (e.g. febrile illness or severe infections), patients on beta blockers or other drugs

Abbreviations: FCPD fibrocalculous pancreatic diabetes mellitus, NPDR nonproliferative diabetic retinopathy, PDR proliferative diabetic retinopathy.

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known to interfere with heart rate responses were excluded. The diagnosis of NIDDM was based on the WHO study group criteria¹⁸ and that of FCPD on the criteria of Mohan.¹⁹ All patients with FCPD had pancreatic calculi on abdominal X-ray and evidence of ductal dilatation on ultrasonography. Twenty healthy age matched non-diabetic subjects chosen from the spouses of patients and staff of the diabetes centre formed the control group.

In all study patients, a complete clinical work up was done including height, weight and blood pressure recording in the right upper limb in the sitting posture. The body mass index (BMI) was calculated using the formula: weight in kg divided by the height in metres squared. Biochemical studies were done on Corning Express Plus Auto Analyser (Corning, Medfield, MA, USA) using kits supplied by Boehringer Mannheim, Mannheim, Germany. Fasting and postprandial plasma glucose (glucose oxidase method), serum cholesterol (CHOD-PAP method), serum triglycerides (GPO-PAP method), and serum creatinine (modified kinetic method of Jaffe) were estimated in all patients. High density lipoprotein (HDL-) cholesterol was estimated by CHOD-PAP method after precipitating low density lipoprotein and chylomicron fractions by the addition of phosphotungstic acid in the presence of magnesium ions and very low density lipoprotein (VLDL-) cholesterol was derived using the Friedewald formula. Low density lipoprotein (LDL-) cholesterol was calculated by total cholesterol - (HDL + VLDL). Glycosylated haemoglobin (HbA_{1c}) was estimated by high pressure liquid chromatography using the Variant machine (Bio Rad, Hercules, CA, USA).

The ocular fundi were examined by a retinal specialist, both by direct and indirect ophthalmoscopy, after mydriasis. Retinopathy when present was classified as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR was diagnosed when there was evidence of microaneurysms, dot haemorrhages, exudates or cotton wool spots in the absence of any new vessels or advanced diabetic eye disease. PDR was diagnosed when any new vessels were present or if there was evidence of fibrous retinitis proliferans, vitreous haemorrhage, retinal detachment or other features of advanced diabetic eye disease.

The following definitions were used for diagnosis of various complications:

Ischaemic heart disease was considered to be present when either myocardial ischaemia or infarction was present.

Myocardial ischaemia was diagnosed if there was a history of exertional chest pain (angina) with unequivocal T wave changes in the electrocardiogram (ECG), but no evidence of infarction.

Myocardial infarction was determined by a history documented by hospital records along with Q wave or

ST/T wave changes on ECG suggestive of a recent or past myocardial infarction.

Dysfunction was defined as bilateral absence of ankle jerks and/or bilateral distal sensory dysfunction. The latter was documented by biothesiometry (Bio Medical Instrument Co., Newbury, Ohio, USA) as previously described.²⁸

Nephropathy was defined as persistent proteinuria of > 500 mmol per 24 h, assessed by the sulphosalicylic acid method,³² in the presence of retinopathy but in the absence of urinary tract infection or other non-diabetic causes of proteinuria. *Renal insufficiency* was defined as serum creatinine > 133 $\mu\text{mol l}^{-1}$.

Autonomic Dysfunction Studies

A battery of five standard tests of autonomic dysfunction, three tests of heart rate responses, and two tests of blood pressure responses to different manoeuvres were done using protocols recommended by Ewing and Clarke³³ and this is outlined in Table 1. The tests were done in the morning in the basal state using a computerized electrocardiograph machine (Fukuda ME, Cardiosun, Japan) with an in-built programme for performing computerized R-R interval analysis. The machine automatically calculates the mean of approximately 100 R-R measurements and provides the minimum R-R, maximum R-R, and the coefficient of variation of R-R (CV of R-R) for each of the parameters tested. For each test, the normal values of the CV of R-R were first determined in the control group and a value below 2 SD of the mean control value was taken as an abnormal test, i.e. indicative of autonomic dysfunction (Table 1).

Autonomic dysfunction when present was classified as normal, early, definite, and severe using a modification of the criteria of Ewing and Clarke³³ as follows.

1. Normal: all five tests normal.
2. Early involvement: one of the three heart rate tests abnormal.
3. Definite involvement: two or more of the heart rate tests abnormal.
4. Severe involvement: two or more of the heart rate tests abnormal plus one or both of the blood pressure tests abnormal.
5. Atypical pattern: any other combination of abnormal tests.

Statistical Analyses

All values are expressed as mean \pm SD. Statistical analyses were done using SPSS programme (version 4.0.1.) on an IBM PC compatible computer. Chi-squared tests were used to compare frequencies and *t*-tests to compare means. Multiple logistic regression analysis was done using autonomic dysfunction as the dependent variable and a host of independent variables including age, duration of diabetes, body mass index, systolic and

Table 1. Normal values for autonomic nervous system tests

	(Coefficient of variation of RR)	
	Control (mean \pm SD)	Abnormal value
<i>Heart rate tests</i>		
Heart rate response to Valsalva	13.2 \pm 5.0	< 3.2
Heart rate variation during deep breathing	11.3 \pm 4.4	< 2.5
Heart rate response to standing	6.5 \pm 2.4	< 1.7
<i>Blood pressure tests</i>		
Blood pressure response to standing (fall in systolic BP)	Less than 10 mm	More than 20 mm
Blood pressure response to sustained handgrip (increase in diastolic BP)	More than 20 mm	Less than 10 mm

diastolic blood pressure, fasting and postprandial plasma glucose, glycosylated haemoglobin, serum cholesterol, and its subfractions LDL, HDL, and VLDL, serum triglycerides, non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, peripheral dysfunction, nephropathy, renal insufficiency, and ischaemic heart disease.

Results

Table 2 shows the clinical details of the subjects studied. There was a male predominance in the FCPD patients compared to NIDDM and the difference, although not large, was statistically significant ($p=0.04$). This is in agreement with the usual sex ratio seen in FCPD

patients.^{19,22} The FCPD patients were also younger and had a lower body mass index compared to the NIDDM patients ($p < 0.001$ for both parameters). There were no significant differences in the duration of diabetes, fasting plasma glucose levels or glycosylated haemoglobin levels between FCPD and NIDDM groups. The serum cholesterol, LDL-cholesterol, VLDL-cholesterol, and serum triglyceride levels were lower in FCPD compared to NIDDM group ($p < 0.001$ for all parameters). There were no significant differences in the occurrence of non-proliferative or proliferative diabetic retinopathy, peripheral dysfunction, nephropathy or renal insufficiency between the NIDDM and FCPD groups, but ischaemic heart disease was more frequent in NIDDM patients ($p < 0.001$).

Table 2. Clinical and biochemical details of study groups

Variable	Controls (n = 20)	NIDDM (n = 336)	FCPD (n = 40)	Significance*
Sex:				
Male	12 (60%)	178 (53%)	28 (70%)	$p = 0.04$
Female	8 (40%)	158 (47%)	12 (30%)	
Age (yr)	48 \pm 10	54 \pm 9	45 \pm 12	$p < 0.001$
Duration of diabetes (yr)	—	9.3 \pm 6.1	10.8 \pm 6.2	NS
Body mass index (kg m ⁻²)	21.9 \pm 3.4	23.0 \pm 2.0	18.0 \pm 1.0	$p < 0.001$
Fasting plasma glucose (mmol l ⁻¹)	4.8 \pm 0.4	10.0 \pm 5.3	11.3 \pm 4.1	NS
HbA _{1c} (%)	6.0 \pm 0.6	9.7 \pm 2.1	10.0 \pm 2.6	NS
Serum cholesterol (mmol l ⁻¹)	5.0 \pm 0.7	5.4 \pm 1.6	4.2 \pm 1.5	$p < 0.001$
HDL-cholesterol (mmol l ⁻¹)	1.3 \pm 0.2	1.1 \pm 0.2	1.1 \pm 0.2	NS
LDL-cholesterol (mmol l ⁻¹)	2.9 \pm 0.6	3.4 \pm 0.9	2.6 \pm 0.5	$p < 0.001$
VLDL-cholesterol (mmol l ⁻¹)	0.8 \pm 0.4	0.8 \pm 0.4	0.5 \pm 0.2	$p < 0.001$
Serum triglyceride (mmol l ⁻¹)	1.2 \pm 0.6	1.9 \pm 1.3	1.2 \pm 0.7	$p < 0.001$
Retinopathy				
NPDR	—	77 (23%)	10 (25%)	NS
PDR	—	12 (3.6%)	1 (2.5%)	NS
Peripheral dysfunction				
Nephropathy	—	95 (28%)	10 (25%)	NS
Renal Insufficiency	—	62 (18.5%)	4 (10%)	NS
IHD	—	14 (4.2%)	1 (2.5%)	NS
		45 (13.3%)	1 (2.5%)	$p < 0.001$

NPDR, non-proliferative diabetic retinopathy;

PDR, proliferative diabetic retinopathy;

IHD, ischaemic heart disease;

*NIDDM vs FCPD.

Table 3. Prevalence of autonomic dysfunction in study groups

	NIDDM (n = 336)	FCPD (n = 40)	Significance
Autonomic dysfunction (total)	120 (35.7%)	9 (22.5%)	$p = 0.19$
Early	88	6	$p = 0.18$
Definite	20	2	$p = 0.91$
Severe	11	1	$p = 0.83$
Atypical	1	—	

40 (12%) of the NIDDM and 4 (10%) of the FCPD patients had one or more symptoms of autonomic neuropathy like postural giddiness, gastrointestinal or bladder disturbances. Table 3 shows the results of the autonomic nervous system tests. The prevalence of autonomic dysfunction was higher in the NIDDM patients compared to the FCPD group but the difference was not statistically significant. There were also no significant differences in the severity of autonomic dysfunction between NIDDM and FCPD patients.

Figure 1 shows the distribution of autonomic dysfunction in relation to the age of the patient. Below the age of 20 years, there was no evidence of autonomic dysfunction either in the NIDDM or in the FCPD groups. Thereafter, there was a steady increase in the prevalence of autonomic dysfunction reaching a peak prevalence of about 50% after 60 years of age in both the groups. Although there was a slight excess of autonomic dysfunction in NIDDM compared to the FCPD group at most age groups, the differences were not statistically significant.

Figure 2 shows the results in relation to the duration of diabetes. In the 0–5 years duration group, 28.2% of NIDDM and 16.6% of FCPD patients had autonomic dysfunction and these figures increased to 56.2% and 60%, respectively, in the 16–20 years duration groups. The differences in prevalence rates between the two groups were not statistically significant.

Logistic regression analyses was done separately in NIDDM and FCPD groups to look for risk factors associated with autonomic dysfunction. In the NIDDM

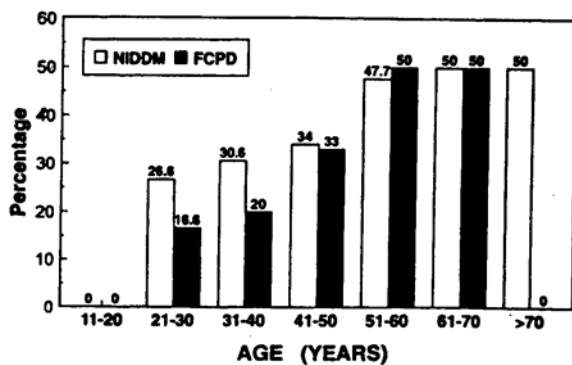


Figure 1. Prevalence of autonomic dysfunction in relation to age of the patients

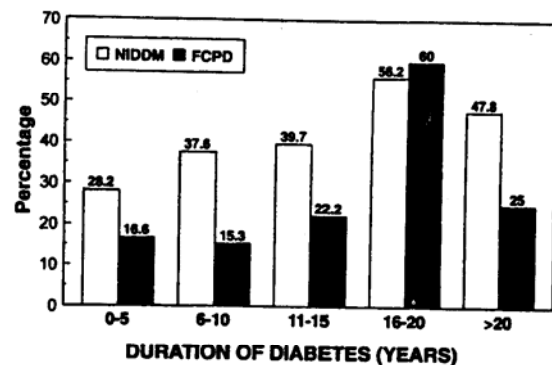


Figure 2. Prevalence of autonomic dysfunction in relation to the duration of diabetes

group, peripheral dysfunction was found to be associated with autonomic dysfunction ($r = 0.66$, $p = 0.02$, odds ratio 1.9, confidence interval 1.09–5.40). There was also an association with proliferative diabetic retinopathy but this failed to reach statistical significance ($p = 0.06$). In FCPD no significant association was found between autonomic dysfunction and any of the variables studied probably because of small sample size.

Discussion

To our knowledge this is the first study on autonomic dysfunction where a primary and a secondary form of diabetes have been compared.

It has been recently proposed that autonomic dysfunction may have an autoimmune basis.^{34–36} An association with iritis has been demonstrated by the King's College Hospital group.³⁵ Rothova *et al.*³⁶ found evidence of anterior uveitis in 12.5% of their patients. Recently, Barzilay *et al.*³⁷ have reported an increased propensity of subjects with HLA DR3/4 to develop autonomic dysfunction. Circulating immune complexes (Ciq) have been found to be elevated³⁸ as well as activated T-lymphocytes.³⁹ The above lines of evidence suggest that autonomic dysfunction is most likely to be found in IDDM and that other types of diabetes would be less susceptible. This prompted us to study two types of diabetes which are not thought to be associated with autoimmunity, namely NIDDM and FCPD.

The present study shows that autonomic dysfunction

is common in both NIDDM and FCPD. It is possible that the actual duration of diabetes is longer in the NIDDM group because of the insidious nature of the disease. In support of this, Ratzmann *et al.*⁴⁰ have recently shown that in a cohort of 'newly diagnosed NIDDM', autonomic dysfunction was seen in 2.1%–7.3% of patients. It is of interest that FCPD, a secondary form of diabetes, also shows evidence of autonomic dysfunction and this suggests that hyperglycaemia, which is the factor common to both diabetic groups, probably plays an important role in the causation of autonomic dysfunction. In the recent Diabetes Control and Complications Trial (DCCT),⁴¹ improvement in autonomic nervous system function was demonstrated in the intensive treatment group, confirming the importance of hyperglycaemia in the pathogenesis of autonomic dysfunction.

Estimates of the prevalence of autonomic dysfunction based on presence of abnormalities of cardiovascular autonomic reflexes have ranged from 14% to 66%.^{2,7–9,42–46} Veglio *et al.*,⁸ in a study of 221 NIDDM patients, found that 66% of patients had at least one abnormal cardiovascular autonomic test. They found a correlation with age but not with duration of diabetes or metabolic control. Jeyarajah *et al.*⁹ observed autonomic nerve function test abnormalities in 46.2% of their NIDDM patients. Ziegler *et al.*⁴⁶ in a large multicentre study involving 22 European diabetes centres found that 16.8% of a cohort of 647 IDDM patients and 22.1% of a cohort of 524 NIDDM patients had definite evidence of cardiovascular autonomic dysfunction. In the only study in the literature on FCPD patients, Govindan and Das³⁰ reported that 5 out of their 23 patients with FCPD (21.7%) had evidence of autonomic dysfunction which is similar to our findings.

Our logistic regression analyses showed an association of autonomic dysfunction with peripheral dysfunction in the NIDDM patients. No association was found with any of the variables tested in the FCPD patients but this probably relates to the small sample size. Other reports^{7,9} have found an association between autonomic dysfunction and age and duration of diabetes. Although we observed an increase in prevalence of autonomic dysfunction with both age and duration of diabetes, this association was not present in the logistic regression analyses. Krolewski *et al.*⁴⁷ have noted an association between proliferative diabetic retinopathy and autonomic dysfunction in patients with IDDM. One study² reported an association between autonomic dysfunction and factors predisposing to macrovascular events, i.e. hypertension, elevation of LDL-cholesterol and a reduction in HDL-cholesterol but this has not been confirmed by other studies.

In summary, we have demonstrated that autonomic nervous dysfunction occurs with similar frequency and severity in NIDDM and FCPD patients. This similarity despite differences in pathogenesis of the underlying disease may suggest a common pathogenic mechanism, probably related to hyperglycaemia.

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