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Vascular complications in long-term South Indian NIDDM of over 25 years' duration

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Abstract

The prevalence of vascular complications was assessed in 726 South Indian non-insulin dependent diabetes mellitus (NIDDM) patients with over 25 years' duration of diabetes. Retinopathy was detected in 52.0% of patients which included 41.7% with non-proliferative and 10.3% with proliferative diabetic retinopathy. Nephropathy was present in 12.7% and neuropathy in 69.8% of patients. While 32.8% of patients had ischaemic heart disease, the prevalence of peripheral vascular disease was only 15.4%. Multivariate logistic regression analyses showed that serum creatinine was associated with retinopathy, creatinine and post-prandial plasma glucose with nephropathy and post-prandial plasma glucose and age with neuropathy. This is one of the first reports on vascular complications in long-term diabetes from the Indian sub-continent.

Keywords: Long-term diabetes; NIDDM; South India; Retinopathy; Nephropathy; Neuropathy; Ischaemic heart disease; Peripheral vascular disease

1. Introduction

It is well known that in patients with long standing diabetes, microangiopathy (retinopathy and nephropathy), neuropathy and macroangiopathy (ischaemic heart disease and peripheral vascular disease) occur with increased frequency [1]. However, there is extreme variability among patients with respect to the time of onset, the prevalence and the severity of the various complications. There are also possible differences in frequency amongst different ethnic groups [2,3].

The prevalence of NIDDM is known to be very high among migrant Asian Indians [4,5] as well as in Indians from the Indian subcontinent [6,7]. It is also of interest that NIDDM in southern India shows several differences from that seen among Europeans. These include stronger genetic factors [8,9], younger age at onset of diabetes [10] and a lower degree of obesity [6]. Given the high prevalence rates of diabetes and these important differences, data on long-term complications in South Indian NIDDM are very valuable. In this report, we present data on the prevalence of vascular complications in a unique cohort of NIDDM with 25 years or more duration of diabetes.

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2. Subjects and methods

2.1. Inclusion criteria

The study group comprised NIDDM patients attending the M.V. Diabetes Specialities Centre (MVDSC) at Madras in southern India who had a known duration of diabetes of at least 25 years. Patients were only included in the study if reliable medical records were available confirming the diagnosis of diabetes, at least 25 years prior to the date of registration of the patient at our centre. Criteria of the WHO study group on diabetes [11] were used for diagnosis of diabetes and classification as NIDDM.

2.2. Clinical assessment

In all study patients a complete clinical work up was done including height, weight and blood pressure estimation 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, USA) using kits supplied by Boehringer Mannheim, Germany. Fasting and post-prandial 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. Glycosylated haemoglobin (HbA1c) was estimated by HPLC method using the Variant instrument (Bio Rad, USA). High density lipoprotein (HDL) cholesterol was estimated by CHOD-PAP method after precipitating low density lipo-protein and chylomicron fractions by the addition of phosphotungstic acid in the presence of magnesium derived using the Friedewald formula. Low density lipoprotein (LDL) cholesterol was calculated by (total cholesterol − (HDL + VLDL)).

Ocular screening included a routine visual acuity examination using Snellen's test charts, ocular pressure recording and biomicroscopic examination of the anterior segment.

2.3. Retinal examination and photography

One drop each of 10% phenylephrine and 1% tropicamide were then administered to both eyes and the best possible mydriasis was obtained. A study of the vitreous cavity and a detailed examination of the retina with the Goldmann three mirror lens or central fundus lens was done wherever necessary. Retinal examination was done by both direct and indirect ophthalmoscopy by a trained retinal specialist (M.R.) who had previously participated in studies in the UK, involving grading of retinal lesions [12].

Retinal photography was performed using a Topcon VT-50 camera. Forty-five-degree stereo photographs were taken of seven standard fields in both eyes. Photographs were graded using a modification of the Hammersmith Hospital Grading System [13]. The Hammersmith Hospital grading system uses a set of standard colour photographs of the retina where the various lesions of retinopathy are graded through different levels of severity from Grade 1 to Grade 5. Diabetic retinopathy was classified as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR was further subdivided into minimal to mild NPDR when only venous changes, microaneurysms or dot haemorrhages were present. If, in addition to microaneurysms or dot haemorrhages, exudates, and/or cotton wool spots were present, they were classified as moderate to severe NPDR. Maculopathy was defined as decrease in visual acuity due to macular oedema in the presence of microaneurysms, haemorrhages or exudates. Proliferative diabetic retinopathy was defined as the presence of abnormal new vessels on the disc (NVD) or elsewhere (NVE). The advanced diabetic eye disease group comprised patients with fibrous retinitis proliferans, vitreous haemorrhage, traction detachment of the retina or optic atrophy.

2.4. Other complications

The following definitions were used for diagnosis of the other complications:

Table 1
Details of the study cohorts according to the duration of diabetes mellitus

Duration of diabetes (years)	Total (n = 726)		Sex distribution	
	Number	Percentage	Males	Females
25–29	403	55.5	290	113
30–34	221	30.4	171	50
35–39	62	8.5	13	49
>40	40	5.5	31	9

Ischaemic heart disease (IHD): 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: A history of myocardial infarction documented by hospital records along with Q- or ST/T-wave changes on ECG suggestive of a recent or past myocardial infarction.

Neuropathy: was defined as bilateral absence of ankle jerks and/or bilateral distal sensory neuropathy. The latter was documented by biothesiometry (Bio Medical Instrument Co., Newbury, OH) by previously described methods [14].

Nephropathy: was defined as persistent proteinuria of more than 300 mg/day in the absence of urinary tract infection or other non-diabetic proteinuria, hypertension or congestive cardiac failure but in the presence of any degree of retinopathy.

Peripheral vascular disease (PVD): was diagnosed clinically if there was a history of intermittent claudication or rest pain and both dorsalis pedis and posterior tibial pulsations were absent in the same foot or one of these pulses was absent in both feet. Doppler studies including a recording of the pressure tracings were done using the KODY Vaslab Machine (Kody Labs, Madras) and the Ankle/Brachial (A/B) index was calculated in all cases. An A/B index of 0.8 or less was defined as PVD by doppler criteria.

2.5. Statistical analysis

Statistical analyses were done using the SPSS program (version 4.0.1) on an IBM PC compatible computer. All values were expressed as mean ± S.D. Comparison of mean values were done using Student's t-test. Multivariate logistic regression analyses was done for each of the complications, i.e. retinopathy, nephropathy, neuropathy, IHD and PVD using that particular complication as the dependent variable. The independent variables tested included fasting plasma glucose, post-prandial plasma glucose, glycosylated haemoglobin, serum cholesterol, serum triglycerides, HDL cholesterol, LDL cholesterol, systolic blood pressure, diastolic blood pressure, age, duration of diabetes, body mass index and serum creatinine.

3. Results

A total of 19 923 NIDDM patients were registered at MVDSC during the years 1992–1995. Of these 726 patients (3.6%) had duration of diabetes of 25 years or more and they formed the cohort for this study. There were 505 males and 221 females. A total of 528 patients (72.7%) had a positive family history of diabetes which included 375 patients (51.7%) with a history of diabetes mellitus in one of their parents.

Table 1 shows a breakdown of the study cohort according to the sex and the duration of diabetes. There was a male predominance in all groups except in those between 35 and 39 years duration.

Table 2 shows the vascular complications in the study group. Retinopathy was present in 378 pa-

Table 2
Vascular complications in long-term diabetic patients (n = 26)

Complication	Number	Prevalence
Retinopathy		
Total	378	52.0%
NPDR	303	41.7%
PDR	75	10.3%
Nephropathy	92	12.7%
Neuropathy	507	69.8%
PVD		
Clinical criteria	88	12.1%
Doppler criteria	112	15.4%
IHD	238	32.8%

NPDR, non proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PVD, peripheral vascular disease; IHD, ischaemic heart disease.

tients (52.0%) which included 303 patients (41.7%) with non-proliferative diabetic retinopathy and 75 patients (10.3%) with proliferative diabetic retinopathy. Nephropathy was detected in 92 patients (12.7%). Peripheral neuropathy was found in 507 patients (69.8%). Clinical evidence of PVD was detected in 12.1% of patients and when doppler criteria was used, the prevalence of PVD rose to 15.4%. Gangrene was present in 15 patients (2.0%) of patients. Ischaemic heart disease was found in 32.8% of patients in this study.

Table 3 shows the breakdown of the complications according to the presence or absence of family history of diabetes. There was no significant difference in the prevalence of retinopathy (NPDR or PDR), nephropathy, neuropathy, PVD or IHD between the two groups.

Table 4 shows the distribution of the various complications according to the treatment received namely diet alone, oral drugs or insulin. There were no significant differences between the three treatment groups with respect to the prevalence of the various complications. Table 5 shows the breakdown of retinopathy according to the duration of NIDDM. It can be seen that there is very little increase in retinopathy prevalence beyond 25 years duration of diabetes.

Table 6 gives the clinical details of the patients with and without retinopathy. Fasting and post-prandial plasma glucose and serum cholesterol levels were significantly higher in the patients with retinopathy compared to those without. It is of interest that the patients with retinopathy were younger than those without.

Table 7 shows the results of the multivariate logistic regression analyses. Only the positive associations are listed in the table. There was an association of retinopathy with serum creatinine, nephropathy with serum creatinine and post-prandial plasma glucose and neuropathy with post-prandial plasma glucose and the age of the patient. There was no association between PVD and IHD with any of the variables studied.

4. Discussion

In this paper, we have presented a study of a unique cohort of NIDDM patients with over 25

Table 3
Breakdown of complications according to family history of diabetes

Complications	Family history of diabetes		Significance
	Yes (n = 528)	No (n = 198)	
Retinopathy			
Total	272 (51.5%)	106 (53.5%)	NS
NPDR	216 (40.9%)	87 (43.9%)	NS
PDR	56 (10.6%)	19 (9.5%)	NS
Nephropathy	66 (12.5%)	26 (13.1)	NS
Neuropathy	368 (69.6%)	139 (70.2%)	NS
PVD (Doppler criteria)	80 (15.1%)	32 (16.1%)	NS
IHD	170 (32.1%)	68 (34.3%)	NS

Table 4
Distribution of complications according to treatment of diabetes[a]

Complications	Total number with complications (n = 726)		
	Diet alone (n = 14)	Oral drugs (n = 172)	Insulin (n = 540)
Retinopathy			
Total (n = 378)	7 (50.0%)	90 (52.3%)	281 (52.0%)
NPDR (n = 303)	5 (35.7%)	80 (46.5%)	218 (40.3%)
PDR (n = 75)	2 (14.3%)	10 (5.8%)	63 (11.6%)
Nephropathy (n = 92)	2 (14.3%)	16 (9.3%)	74 (13.7%)
Neuropathy (n = 507)	8 (57.1%)	147 (85.4%)	352 (65.1%)
PVD (n = 112) (Doppler criteria)	2 (14.3%)	18 (10.4%)	92 (17.0%)
IHD (n = 238)	3 (21.4%)	73 (42.4%)	162 (30.0%)

[a]None of the differences were statistically significant.

years of diabetes. A study of this nature inevitably suffers from the drawback that it is confined to the survival cohort and many patients might have succumbed earlier to diabetic complications. Although clinic based, our study has the strength that it is based on large numbers of patients and is based on sensitive screening techniques.

Although there are little comparable data from within India, there are a number of reports from abroad. Retinopathy was noted in 65% of adult onset diabetes of over 25 years duration who were examined at the Joslin Clinic for the Diabetes Natural History Study [1]. A similar study done in Oklahoma Indians with NIDDM of over 25 years duration showed a prevalence rate of 60% [15]. The prevalence rate for proliferative retinopathy in the Joslin Clinic series was 15% [1] while in the Oklahoma Indians study it was 20% [15]. In a unique long-term follow-up study, Pirart [16] found 70% of a cohort of NIDDM patients had non-proliferative retinopathy and 10% had proliferative retinopathy.

The prevalence rates of retinopathy from various studies across the world have been compiled by Ekoe [17]. In most studies there appears to be an increase in prevalence of retinopathy up to about 20 years of diabetes duration and thereafter there is a plateau. This plateau could be explained by a decline in the diabetic retinopathy incidence rates and/or an increase in the frequency of the renal-retinal syndrome which is associated with a high mortality.

Both fasting and post-prandial plasma glucose levels were significantly higher in the retinopathy group in this study. While glycosylated haemoglobin levels were also higher, the difference was not statistically significant. In the Wisconsin Epidemiology Study of Diabetic Retinopathy, Klien et al.[18] have also shown the impact of hyperglycaemia on development of retinopathy. The recently published DCCT study [19] has conclusively proved the benefits of good control of diabetes on the incidence and progression of retinopathy.

It is interest that nearly one third of patients were free of retinopathy after 40 years of diabetes. This observation supports recent observations that genetic factors may play a role in the pathogenesis of diabetic retinopathy [20,21].

A higher rate of renal disease in Asian compared to European diabetic patients has been reported by other workers [22,23]. We found proteinuria in 12.7% of our patients. This is higher than the prevalence rate of 7% reported by Wirta et al. [24] in a group of long-term European NIDDM. It is possible that many of our patients with nephropathy could have died.

Ischaemic heart disease (IHD) has been found to be more common among Asian Indians in the UK [25–27]. It is possible that the prevalence of IHD could have been much higher than seen in this survival cohort. This is supported by several lines of evidence. Firstly, IHD occurs at a much younger age in Asian Indians [25]. Secondly, it is

Table 5
Breakdown of retinopathy according to the duration of NIDDM

Duration of diabetes	Total (n = 726)	Any DR (n = 378)	NPDR (n = 303)	PDR (n = 75)
25–29	403	217 (53.8%)	170 (42.2%)	47 (11.6%)
30–34	221	111 (50.2%)	93 (42.1%)	18 (8.1%)
35–39	62	30 (48.4%)	23 (37.1%)	7 (11.3%)
40	40	20 (50.0%)	17 (42.5%)	3 (7.5%)

DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 6
Clinical details of long-term diabetics with and without retinopathy

Variable	No retinopathy (n = 348)	Some retinopathy (n = 378)	Significance
Age (years)	70 ± 8	65 ± 7	$P < 0.001$
Age at onset of diabetes (years)	36 ± 8	35 ± 7	NS
Duration of diabetes (years)	30 ± 6	30 ± 4	NS
Fasting plasma glucose (mg/dl)	167 ± 64	204 ± 78	$P < 0.001$
Post-prandial plasma glucose (mg/dl)	253 ± 76	298 ± 92	$P < 0.001$
Serum cholesterol (mg/dl)	196 ± 40	210 ± 46	$P = 0.001$
Serum triglycerides (mg/dl)	154 ± 82	161 ± 79	NS
HDL cholesterol (mg/dl)	45 ± 13	44 ± 11	NS
Glycosylated haemoglobin (%)	9.7 ± 2.3	10.1 ± 2.3	NS

Table 7
Multivariate logistic regression analyses for complications

Dependent variable	Variable tested	Regression co-efficient (b)	SE (b)	P-value	Odds Ratio (95% CI)
Retinopathy	Creatinine	0.23	0.11	0.04	1.26 (1.01–1.57)
Nephropathy	Creatinine	0.95	0.22	<0.001	2.57 (1.66–3.99)
	Post-prandial plasma glucose	1.01	0.39	0.01	2.74 (1.27–5.92)
Neuropathy	Post-prandial plasma glucose	0.58	0.24	0.01	1.79 (1.13–2.85)
	Age	0.60	0.23	0.01	1.83 (1.17–2.85)

S.E., standard error; C.I., confidence intervals.

well known that survival rates after a heart attack are lower for those with diabetes compared to those without diabetes [28,29]. Thirdly, the rates for IHD in this study are based on symptomatic IHD only and it is possible that some patients may have silent ischaemia. Indeed, treadmill tests done by us in a recent study of young asymptomatic NIDDM patients showed very high rates of IHD [30]. Duc to advanced age of our study cohort, treadmill tests were not done.

This study confirms our earlier observations [31] and that of others [3,32] that PVD is less common among Indian NIDDM compared to Europeans [33]. The reason why the frequency of ischaemic heart disease should be higher and peripheral vascular disease (another form of macroangiopathy) lower in Asian Indian diabetic patients remains unclear.

The prevalence of diabetic neuropathy varies considerably in different studies because of differences in the definition, method of assessment and

patient selection. Pirart [17] using clinical methods reported a prevalence rate of 7.5% at the time of diagnosis which increased to approximately 50% after 25 years duration of diabetes. In our study we found 70% of patients had clinical evidence of neuropathy. The higher prevalence of neuropathy in our series could be explained by the older age group of the patients and the use of biothesiometry to assess neuropathy.

In summary, we present a study of the prevalence of vascular complications in long-term South Indian NIDDM patients. It is clear that many patients with long-term diabetes escape from serious vascular complications. The search for 'protective factors' (genetic or other) in long-term diabetic patients who are free of complications may throw light on the pathogenesis of these complications.

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