Microvascular complications in South African patients with long-duration diabetes mellitus

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Objective. To determine the prevalence of microvascular complications in South African black and Indian patients with long-duration diabetes mellitus (DM).

Design. A retrospective analysis was undertaken of clinical records of 219 DM patients (132 black, 87 Indian) with long-duration DM (over 10 years) attending a diabetes clinic in Durban. Data recorded on each subject included demographic details (age, gender, ethnic group, type of diabetes, age of onset and duration of diabetes), presence of retinopathy, markers of nephropathy and biochemical variables. The prevalence of complications and the clinical and biochemical parameters were evaluated for type 1 and type 2 diabetes and for each ethnic group.

Results. Of the 219 patients, 47 had type 1 DM (36 blacks, 11 Indians) and 172 were classified as type 2 DM (96 blacks, 76 Indians). The mean age of onset of DM was later in blacks than Indians, both for type 1 ($P < 0.05$) and type 2 DM ($P < 0.01$). In patients with type 1 DM, the prevalence of retinopathy was 53.2% (blacks 55.6%, Indians 45.5%), persistent proteinuria was found in 23.4% (blacks 25%, Indians 18.2%) and hypertension in 34%. No ethnic difference was found except for the prevalence of hypertension which was higher in blacks than Indians (41.7% v. 9.1%, $P < 0.5$). Onset of retinopathy from time of diabetes diagnosis occurred earlier in blacks than Indians (13.0 ± 4.6 yrs v. 18.0 ± 4.6 yrs, $P < 0.05$). For the type 2 DM group, retinopathy was found in 64.5% (black v. Indian 68.8 v. 59.2%) and persistent proteinuria in 25% (black v. Indian 30.2 v. 18.4%). Hypertension was observed in 68% and was more prevalent in blacks (84.4 v. 47.4%, $P < 0.01$) There was an earlier onset of retinopathy ($P < 0.05$) and hypertension ($P < 0.01$) from time of diabetes diagnosis in blacks than Indians. In the type 1 DM group retinopathy was associated with a significantly

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longer duration of diabetes ($P < 0.05$) and higher glycated haemoglobin (HbA_1) ($P < 0.05$). For type 2 DM subjects there was a significant association between retinopathy and longer duration of diabetes ($P < 0.05$) and higher systolic blood pressure ($P < 0.05$).

Conclusion. This study has shown that there is a high prevalence of microvascular complications in South African patients with long-duration diabetes mellitus.

S Afr Med J 2001; **91:** 987-992.

Traditionally diabetes mellitus (DM) has been regarded as a disease of urbanisation and industrialisation, and one that is still rare or unknown in rural Africa.[1,2] But, based on World Health Organisation (WHO) criteria and age-standardised estimates, King and Rewers[2] have shown that diabetes in adults is a global problem and that populations in developing countries, minority groups and disadvantaged communities in industrialised countries face the greatest risk. Data on diabetes epidemiology in Africa have shown that although the prevalence is low in some rural communities, in other countries there is a moderate prevalence comparable with that found in developed countries.[3]

It is well established that there is increased morbidity and mortality associated with diabetes complications, both microvascular and macrovascular. The natural history and clinical course of diabetes in Africa is poorly understood, in many instances because of poor follow-up.[1] Earlier reports have indicated that unlike in Western populations where the major causes of mortality were cardiovascular and renal disease, in Africa the major aetiological factors were acute metabolic and infective.[1,4-6] More recently, reports from Ethiopia[7] and South Africa[8] have indicated a changing pattern, with diabetic nephropathy playing a more important role in mortality.

In Western countries the prevalence of retinopathy ranges from 2% to 90% and that of nephropathy from 2% to 20% depending on type and duration of diabetes.[9] Reports on prevalence of macrovascular complications in Africa are limited. Previous impressions that microvascular complications are rare in Africa were probably related to shorter survival rates and inadequate screening.[1] Earlier studies (before 1990) from Africa have reported that the prevalence of retinopathy was 2.9 - 57.1% and that of nephropathy 1.0 - 30.5%;[1] however, such studies involved mixed cohorts of type 1 and type 2 diabetes patients with varying duration of disease.

Although several studies have examined subjects with diabetes duration of 10 years or more, only three reports on well-defined groups have examined diabetes outcome.[7,8,10] Such studies showed that in type 1 diabetes[7,8] retinopathy was found in 40 - 50% and nephropathy in 20 - 28%. In Ethiopian type 2 patients with DM duration over 20 years, retinopathy was found in 45.5% and nephropathy in 29.8% of cases.[10]

In a recent report[11] of an audit of primary health care services in Cape Town, a high prevalence of complications was found; however, again this report included both type 1 and type 2 diabetes patients and with varying duration of disease.

This retrospective analysis was undertaken to determine the prevalence of retinopathy and nephropathy in South African blacks and Indian patients with diabetes duration of over 10 years.

PATIENTS AND METHODS

Patients and background

The study population comprised South African black and Indian patients with diabetes duration over 10 years registered at the diabetes clinic at King Edward VIII Hospital (KEH), Durban. KEH is the major referral hospital not only for the city but also for the province of KwaZulu-Natal which represents a quarter of the total population of the country.

Patients are reviewed at the diabetes clinic at monthly, 3-monthly or 4-monthly intervals. At each visit symptomatic details are recorded. Clinical examination includes measurement of weight, blood pressure (BP) and pulse rate; dipstix urine is examined for glucose, protein and ketones; capillary blood glucose is measured with reflectance meter and venous blood samples are taken for estimation of glycated haemoglobin, plasma glucose, serum fructosamine, serum lipids, urea and electrolytes. Annually, fundal examination, visual acuity and glomerular filtration rate (GFR) are assessed. Records of such information are available from 1983.

Methods

Using November 1995 as the reference end-point of the study, information was obtained on demographic data, presence or absence of retinopathy and markers of nephropathy and biochemical variables. Demographic details included the following: age, gender, ethnic group, type of diabetes, age of onset and duration of diabetes and the date of the last clinic visit if the subject was lost to follow-up.

The information recorded regarding retinopathy included presence or absence of retinopathy; if present, whether it was background or proliferative; use of laser treatment and estimation of duration from time of diabetes diagnosis to the onset of retinopathy.

The markers of diabetic nephropathy evaluated included persistent dipstix proteinuria, hypertension, serum creatinine and GFR. The presence or absence of proteinuria over the previous six visits (18 months) was recorded. The means of three values per year for systolic and diastolic BP were calculated. A record was kept of hypertension requiring treatment from the time of diabetes diagnosis. Hypertension

w s defined using WHO criteria,[12] i.e. systolic BP ≥ 160 mmHg or diastolic BP ≥ mmHg or if the patient was receiving antihypertensive treatment; borderline hypertension was defined as BP > 140/90 mmHg but < 160/95 mmHg. The most recent serum creatinine and GFR measurements and their duration from time of diabetes onset were noted.

The means of three values per year were calculated for finger prick capillary glucose, venous plasma glucose, HbA_1 (before 1993) and HbA_{1c} (after 1993). Retinopathy was evaluated by the record of findings at annual fundal examination done through dilated pupils using hand-held monocular direct ophthalmoscopy. Retinopathy was classified as background, pre-proliferative or proliferative.[13]

Persistent proteinuria was defined as dipstix proteinuria on three or more consecutive occasions over 18 months in the absence of infection or cardiac failure, serum creatinine was defined as abnormal if the value was > 115 µmol/l at the last visit, and abnormal GFR was defined if GFR < 95 ml/min in women and GFR < 98 ml/min in men.

Biochemical tests

The methods used for the biochemical variables were as follows: venous plasma glucose was measured using a glucose oxidase method; cation exchange microcolumn chromatography for HbA_1 (normal range 5 - 8%); enzyme-linked immunosorbent assay (ELISA) technique for HbA_{1c} (normal range 3.5 - 5.6%); serum creatinine was measured by reaction rate (normal range 53 - 115 µmol/l). GFR was assessed using ^{99M}Tc- DTPA (normal range 98 - 150 ml/min for men, 95 - 12 ml/min for women).

Statistical analysis

Statistical analysis was performed using the SAS computer programme.[14] The prevalence of complications and the clinical and biochemical parameters were evaluated for type 1 and type 2 diabetes and for each ethnic group. Data are expressed as means ± standard deviations (SD) or prevalence (%). Ethnic differences were assessed using the unpaired Student's *t*-test for numerical data and the chi-square test for categorial data. A *P*-value < 0.05 was regarded as significant.

RESULTS

The study group comprised 219 patients (159 women, 60 men; 132 blacks, 87 Indians) identified as having had diabetes for over 10 years and who constituted 25.2% of the 870 patients registered at the diabetes clinic. Of these, 172 subjects (78.5%) had type 2 diabetes and 47 (21.5%) had type 1 diabetes.

Clinical characteristics

Table I shows the clinical and biochemical characteristics. In both the type 1 and type 2 diabetes groups the mean age of onset was later in black than Indian patients ($P = 0.03$, type 1; $P = 0.004$, type 2), and BP was higher ($P < 0.05$). While BP control appeared reasonable, overall glycaemic control, as judged by glycated haemoglobin level, was suboptimal in both ethnic groups.

Prevalence of complications (Table II)

In the type 1 diabetes group retinopathy was found in over half of the patients; the mean onset of retinopathy from time of

Table I. Clinical and biochemical characteristics of 219 subjects with long-duration diabetes mellitus (DM) (> 10 yrs)*

	Type 1 diabetes				Type 2 diabetes			
Variable	Total	Black	Indian	*P*-value	Total	Black	Indian	*P*-value
Number	47	36	11	-	172	96	76	-
Gender (F/M) (*N*)	28:19	22:14	6:5	-	131:41	72:24	59:7	-
Age (yrs)	39.5 ± 10.9	39.9 ± 11.2	38.0 ± 10.5	0.6	58.4 ± 9.4	59.1 ± 7.8	57.4 ± 11.0	0.3
Age of onset (yrs)	22.5 ± 11.0	24.3 ± 11.4	16.6 ± 7.4	0.03	39.9 ± 9.4	41.8 ± 8.0	37.5 ± 10.5	0.004
Duration (yrs)	16.10 ± 4.9	15.6 ± 3.6	21.3 ± 6.8	0.005	18.6 ± 5.7	17.4 ± 4.9	20.2 ± 6.2	0.002
Lost to follow-up (*N* (%))	16 (34)	9 (25)	7 (63.6)	0.07	57 (33.1)	32 (33.3)	25 (32.9)	0.1
Blood pressure (mmHg)								
Systolic	133 ± 13.6	135.3 ± 12.5	125.9 ± 15.4	0.04	144.7 ± 13.3	147.2 ± 12.8	141.4 ± 13.5	0.0052
Diastolic	82.1 ± 8.1	83.5 ± 7.8	77.7 ± 2.8	0.03	84.4 ± 8.4	86.7 ± 8.2	81.4 ± 7.9	0.0001
Plasma glucose (mmol/l)	10.8 ± 4.2	11.5 ± 4.1	8.2 ± 3.5	0.02	12.1 ± 3.9	12.1 ± 4.7	12.1 ± 3.4	0.0195
HbA_1 (%)‡	9.5 ± 1.5	9.9 ± 1.5	9.5 ± 1.4	0.5	9.7 ± 1.8	10.0 ± 2.1	9.3 ± 1.4	0.02
HbA_{1c} (%)§	9.8 ± 2.2	10.2 ± 2.3	8.6 ± 1.6	0.08	9.8 ± 2.1	9.8 ± 2.2	9.8 ± 2.1	0.1
Serum creatinine (µmol/l)	99.2 ± 77.1	95.7 ± 68.5	111.5 ± 105.2	0.6	132.4 ± 174.5	147.2 ± 212.7	113.6 ± 106.2	0.2
Glomerular filtration rate (ml/min)	98.6 ± 33.9	98.5 ± 31.5	99.1 ± 42.9	0.9	77.0 ± 32.9	74.6 ± 32.1	80.1 ± 34.1	0.2

* Data are means ± SD, except as noted.
† P-value: Black v. Indian.
‡ $N = 43$, type 1; $N = 149$, type 2.
§ $N = 30$, type 1; $N = 123$, type 2.

Table II. Prevalence of microvascular complications in 219 patients with diabetes mellitus (DM), duration > 10 yrs (% (*N*))

	Type 1 DM (% (*N*))				Type 2 DM (% (*N*))			
	Total (*N* = 47)	Black (*N* = 36)	Indian (*N* = 11)	*P*-value†	Total (*N* = 172)	Black (*N* = 96)	Indian (*N* = 76)	*P*-value†
Retinopathy								
Any	53.2 (25)	55.6 (20)	45.5 (5)	0.6	64.5 (111)	68.8 (66)	59.2 (45)	0.2
Background only	38.3 (18)	38.9 (14)	36.4 (4)	0.6	44.2 (76)	47.9 (46)	39.5 (30)	0.2
Proliferative	14.9 (7)	16.7 (6)	9.1 (1)	0.5	20.4 (35)	20.8 (20)	19.7 (15)	0.9
Laser treatment	17.0 (8)	16.7 (6)	18.2 (2)	0.9	29.7 (51)	26.0 (25)	34.2 (26)	0.2
Onset from DM diagnosis (yrs)*	14 ± 4.9	13.0 ± 4.6	18.0 ± 4.6	0.039	14.4 ± 6.0	13.1 ± 4.9	16.2 ± 7.0	0.01
Proteinuria								
Persistent (p.p)	23.4 (11)	25.0 (9)	18.2 (2)	0.6	25.0 (43)	30.2 (29)	18.4 (14)	0.08
Without retinopathy	0 (0)	0 (0)	0 (0)	-	13.9 (6)	10.4 (3)	21.4 (3)	0.06
Onset from DM diagnosis (yrs)*	11.4 ± 3.2	10.3 ± 2.1	16.5 ± 2.1	0.0045	13.4 ± 4.8	13.5 ± 4.7	13.4 ± 4.9	0.9
Hypertension								
Requiring treatment	34.0 (16)	41.7 (15)	9.1 (1)†	0.046	68.0 (117)	84.4 (81)	47.4 (36)	0.001
BP ≥ 160/95 mmHg	10.6 (5)	11.1 (4)	9.1 (1)	0.9	19.1 (31)	23.9 (22)	12.7 (9)	0.07
BP ≥ 130/85 mmHg	57.5 (27)	66.7 (24)	27.3 (3)	0.021	90.2 (148)	92.5 (86)	87.3 (62)	0.001
Onset from DM diagnosis (yrs)*	9.6 ± 3.5	9.3 ± 0.3	14.0 ± 0	0.2	13.1 ± 7.1	11.7 ± 6.0	16.3 ± 8.2	0.001
Abnormal serum creatinine‡	17.8 (8)	17.1 (6)	20.0 (2)	0.8	25.2 (43)	29.2 (28)	20.0 (15)	0.2
Glomerular filtration rate (ml/min)								
< 95 (women), < 98 (men)	39.5 (17)	39.4 (13)	40.0 (4)	0.9	73.4 (124)	73.4 (69)	73.3 (55)	0.9
< 70	20.9 (9)	18.0 (6)	30.0 (3)	0.4	42.0 (71)	46.8 (44)	36.0 (27)	0.2

* Mean ± SD.
† *P*-value: black v. Indian.
‡ > 115 µmol/l.

diagnosis was significantly earlier in blacks than Indians (13.0 ± 4.6 yrs v. 18.0 ± 4.6 yrs, $P = 0.039$). Nephropathy on the basis of persistent proteinuria was found in approximately one-quarter of the subjects, all of whom had retinopathy. One-third of the patients had hypertension requiring treatment and the prevalence was higher in blacks than Indians (41.7% v. 9.1%, $P = 0.046$); 17.8% of patients had elevated serum creatinine and 20.9% had abnormal GFR.

In the type 2 diabetes group the prevalence of retinopathy was 64.5%; the mean onset of retinopathy from time of diagnosis was significantly earlier in blacks than Indians (13.1 ± 4.9 yrs v. 16.2 ± 7.0 yrs, $P = 0.01$. Nephropathy based on persistent proteinuria was found in 25% of these patients; 6 (3.5%) had no retinopathy. Hypertension was observed in 68%, with a higher prevalence in blacks than Indians (84.4% v. 47.4%, $P = 0.001$); the mean onset from time of diagnosis was earlier in blacks than Indians (11.7 ± 6.0 yrs v. 16.3 ± 8.2 yrs, $P = 0.001$) An elevated serum creatinine was found in 25.2% and abnormal GFR in 42% of type 2 diabetes patients.

Risk factors and complications (Table III)

Analysis of known risk factors for microvascular complications showed that in type 1 DM subjects retinopathy was associated with significantly longer duration of diabetes ($P = 0.046$) and higher HbA_1 ($P = 0.028$). For the type 2 DM group, when compared with subjects without retinopathy, the duration of diabetes was longer ($P = 0.04$) and systolic BP higher ($P = 0.0125$) in subjects with retinopathy.

Discussion

This study of South African black and Indian patients with long-duration (> 10 years) type 1 and type 2 DM shows an increased prevalence of retinopathy and nephropathy. Ethnic comparisons demonstrate that the prevalence of hypertension was higher and the onset of retinopathy earlier in blacks than Indians.

It is difficult to compare the results of this study with other studies from Africa since most studies have examined mixed cohorts of type 1 and type 2 diabetes patients, with varying duration of disease.[1]

For type 1 diabetes comparison is only possible with two outcome studies from Africa.[7,8] When compared with the recent South African report of 36 patients with mean diabetes duration of 13 years, the prevalence of retinopathy is similar (53.2% v. 52%), persistent proteinuria lower (23.4% v. 28%) and hypertension higher (34% v. 22%).[8] In Ethiopian subjects, Lester[7] reported prevalence rates of 40.7% for retinopathy and 20% for persistent proteinuria and hypertension respectively in a cohort of patients with diabetes duration of over 10 years. The apparent low prevalence rates in other African studies is probably accounted for by the varying diabetes durations of

Table III. Relationship between microvascular complications and known risk factors in 219 patients with long-duration diabetes mellitus (DM)

	Type 1 DM (N = 47)				Type 2 DM (N = 172)			
	Retinopathy		Persistent proteinuria		Retinopathy		Persistent proteinuria	
Risk factor	Yes	No	Yes	No	Yes	No	Yes	No
Blood pressure (mmHg)								
Systolic	133.6 ± 13.9	132.5 ± 13.7	140.8 ± 17.1	130.1 ± 0.9	146.6 ± 12.9	141.3 ± 13.6†	146.9 ± 11.8	143.3 ± 14.0
Diastolic	80.7 ± 7.5	83.7 ± 8.7	85.6 ± 8.2	80.8 ± 7.8	84.8 ± 7.8	83.7 ± 9.4	85.6 ± 7.8	83.7 ± 8.8
Capillary glucose (mM)	10.8 ± 2.4	10.2 ± 3.2	10.5 ± 2.3	10.5 ± 2.9	11.7 ± 2.6	11.7 ± 2.5	11.7 ± 2.9	11.7 ± 2.4
Plasma glucose (mM)	11.7 ± 4.3	9.8 ±3.9	10.7 ± 3.3	10.8 ± 4.5	12.4 ± 3.5	11.5 ± 4.5	11.9 ± 4.0	12.2 ± 3.8
HbA_1 (%)	10.2 ± 1.7	9.2 ± 0.8†	10.3 ± 2.3	9.6 ± 0.9	9.9 ± 2.0	9.4 ± 1.5‡	9.6 ± 1.7	9.8 ± 1.9
HbA_{1c} (%)	10.1 ± 2.3	9.5 ± 2.2	10.2 ± 2.8	9.7 ± 2.0	9.9 ± 1.9	9.6 ± 2.4	10.2 ± 2.3	9.6 ± 1.9
Age of onset (yrs)	23.6 ± 10.8	21.2 ± 11.5	23.2 ± 10.4	22.2 ± 11.4	40.2 ± 9.8	39.5 ± 8.8	39.2 ± 9.0	40.3 ± 9.7
Diabetes duration (yrs)	18.3 ± 5.2	15.4 ± 4.3†	17.4 ± 6.3	16.8 ± 4.4	19.2 ± 6.2	17.6 ± 4.3†	19.2 ± 5.1	18.3 ± 5.9

Data are means ± SD.
† $P < 0.05$: yes v. no.
‡ $P = 0.052$: yes v. no.

the subjects studied and possibly shortened survival rates.[1] The observed prevalence of retinopathy and persistent proteinuria in this study is compatible with reports from the Western literature.[9,13,15]

It is interesting that although no ethnic difference was observed for the prevalence of retinopathy and persistent proteinuria, hypertension was more prevalent in blacks than Indians. This finding is in contrast with earlier reports on patients with shorter duration type 1 diabetes which showed no ethnic difference,[16] but it is compatible with other reports which highlight the high prevalence of hypertension in black Africans[1] and with epidemiological evidence indicating that in South Africa hypertension is more prevalent in blacks (25%) than Indians (14%).[17]

The finding of later onset of diabetes in blacks than Indians is compatible with previous South African studies in which onset was found to be later in blacks than Indians[16,18] and Europids.[19] However, studies from North America found similar age of onset in black and white children.[20]

Despite the later onset of diabetes, the onset of retinopathy from time of diagnosis was earlier in blacks than Indians. The reasons for this are unclear since there was no difference in glycaemic control between the two groups. It is possible, however, that the higher prevalence of hypertension in blacks is responsible for the acceleration of retinopathy.

In type 2 diabetic subjects the prevalence of retinopathy and persistent proteinuria is similar to rates reported in the Western literature.[9,13,15] As for type 1 diabetes, comparison with other African studies is difficult because of mixed cohorts of type 1 and type 2 diabetes and varying diabetes duration in such studies.[1] Notwithstanding, in the Ethiopian report[10] on 121 predominantly type 2 patients with diabetes of over 20 years' duration the prevalence of retinopathy (45.5%) was lower than in this study, while that of persistent proteinuria (29.8%) was similar. The lower prevalence of retinopathy (55.4%) and persistent proteinuria (5.3%) found in a recent audit of South African blacks can be explained by the varying duration of diabetes in the patients studied (mean duration 8 years, range 0 - 28 years); moreover, that report included type 1 subjects.[11] Ethnic difference was only observed for prevalence of hypertension, which was higher in blacks than in Indians and might reflect the high background prevalence in blacks.[17]

As for type 1 diabetes, the onset of retinopathy from time of diagnosis was earlier in blacks than Indians; the difference may be accounted for by the higher BP levels in black patients. What is also apparent from this analysis is that in the group as a whole glycaemic control is poor; this clearly highlights the need for more aggressive intensive management to optimise control.

In conclusion, this study has shown that in South African black and Indian patients with long-duration diabetes there is a high prevalence of microvascular complications. Previous impressions that microvascular complications are rare in Africa were probably related to shorter survival rates and inadequate screening; as survival rates improve and there are greater numbers of African patients with long-duration diabetes, the pattern will probably be similar to that observed in the Western world.

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Accepted 9 September 2001.