

CHAPTER VII

DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE

A REVIEW OF SOUTH AFRICAN STUDIES

Dr NS Levitt, Professor WF Mollentze

DEFINITION, CLASSIFICATION AND DIAGNOSIS OF DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE

Diabetes mellitus, the commonest metabolic disorder worldwide, is characterised by chronic hyperglycaemia, disordered carbohydrate, lipid and protein metabolism and is associated with the development of specific microvascular complications and non-specific macrovascular disease.¹ Major differences in the clinical expression of diabetes have been appreciated for over a 100 years. It is only recently, however, that with increasing knowledge of the aetiology and pathogenesis of diabetes, albeit incomplete, the heterogeneity of the disease has become apparent. This has led to the suggestion that diabetes is not a single disease but a syndrome.

The current internationally accepted classification of diabetes mellitus and other categories of glucose intolerance was published as a part of a technical report by the World Health Organisation in 1985 (Table I).² This classification was largely based on the National Diabetes Data Group's provisional consensus classification.³ The report also provided standard diagnostic criteria and a terminology suitable for clinical and epidemiological research, which have been adopted widely.¹

Impaired glucose tolerance (IGT) is defined as a glycaemic response to a standard oral glucose challenge (75 g) intermediate between normal and diabetes in the presence of a normal fasting blood glucose level and can therefore only be determined by an oral glucose tolerance test (OGTT).² For epidemiological studies the 2-hour value alone may be adequate for the diagnosis of diabetes mellitus.

Much controversy surrounds the subject of IGT.⁴ The variability of the blood glucose response to a glucose load was emphasised by Yudkin, *et al.*⁵ They cited examples of 20-35% coefficients of variation in the 2-hour blood glucose concentration. (Studies are urgently needed to clarify the meaning of IGT especially in black populations.)

Long-term follow-up studies have also shown a change in glucose tolerance over time. In the 10-year follow-up of the Bedford survey in England, 15% of 241 people with 'borderline diabetes' worsened to diabetes while 53% substantially improved their glucose tolerance.⁶ The risk of progression to diabetes was predicted by the degree of glucose intolerance while obesity also had a delayed predictive value which only manifested after 5 years. IGT was thus clearly a heterogeneous and unstable category. The long-term outcome of IGT in black patients still has to be clarified.

Despite its apparent variability, IGT appears to confer an increased risk of coronary heart disease (CHD). In the Whitehall study 281 men, aged 40 - 60 years, with IGT were followed for 7,5 years for cardio-respiratory disease.⁷ CHD mortality doubled when the 2-hour blood glucose concentration

Naomi S Levitt (M.D.) is a Senior Specialist in the Endocrine and Diabetes Unit, Dept of Medicine at the University of Cape Town and Groote Schuur Hospital. She has particular interest in the epidemiology of diabetes and its complications, and in diabetes health care.

Willie F Mollentze (M.Med., F.C.P. (S.A.)), previously professor in the Department of Internal Medicine at the University of the Orange Free State, Bloemfontein, is in private practise at present. He has a special interest in the epidemiology of diabetes.

exceeded the 95th percentile (5,4 mmol/l).

Table I. WHO (1985)² classification of diabetes mellitus and allied categories of glucose intolerance

A. Clinical classes

Diabetes mellitus (DM)

* Insulin-dependent diabetes mellitus (IDDM)

* Non-insulin dependent diabetes mellitus (NIDDM)

(a) Non-obese

(b) Obese

* Malnutrition-related diabetes mellitus (MRDM)

* Other types of diabetes associated with certain conditions and syndromes: (1) pancreatic disease; (2) disease of hormonal aetiology; (3) drug-induced or chemical-induced conditions; (4) abnormalities of insulin or its receptors; (5) certain genetic syndromes; (6) miscellaneous.

Impaired glucose tolerance (IGT)

(a) Non-obese

(b) Obese

(c) Associated with certain conditions and syndromes

Gestational diabetes mellitus (GDM)

B. Statistical risk classes (subjects with normal glucose tolerance but substantially increased risk of developing diabetes)

Previous abnormality of glucose tolerance

Potential abnormality of glucose tolerance

The major clinical classes include diabetes mellitus (insulin-dependent and non-insulin-dependent), impaired glucose tolerance and gestational diabetes.

**PREVALENCE OF DIABETES MELLITUS IN SOUTH AFRICAN POPULATIONS
INSULIN DEPENDENT DIABETES MELLITUS (IDDM)**

The basis for the distinction between the major subclasses of diabetes mellitus is the patient's dependence for survival on insulin. Such dependence is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with greatly raised concentrations of glucose and ketone bodies in the blood and urine.² Insulin treatment is necessary, not only to control hyperglycaemia, but to prevent spontaneous ketosis and death.¹ In some non-Euripids, it may be difficult to distinguish between IDDM and NIDDM and classification difficulties may be encountered in 20-30% of patients.²

There are no accurate data of the frequency or incidence of IDDM in South Africa. The low prevalence of IDDM worldwide compared to NIDDM necessitates large population samples to obtain reliable data.² Previously, IDDM was regarded as being extremely rare in black children in the first decade of life and in schoolchildren.⁸ Walker commented on surveys where 'thousands' of black schoolchildren were screened for glycosuria and all were negative.⁹ It has been suggested that due to the rapidity of onset of symptoms, death ensued before the patient could present to hospital.¹⁰ It is doubtful whether this view is accurate for most regions in South Africa.

Although diabetes was not uncommon among young Indian subjects, Jackson¹¹ emphasised that they seldom became keto-acidotic, indicating the rarity of IDDM in this group. In a recent survey of 2 479 Indians, 15 years and older, Omar, *et al.*¹² found that only 2,2% of the 183 known diabetes patients were on insulin. In a study at King Edward Hospital in Durban, Indian IDDM subjects accounted for 1,1% of the total diabetes clinic population, and black IDDM subjects for 10,4%.¹³

A number of centres have reported on the proportion of their clinic populations that comprise insulin-dependent diabetes patients. Gill and Huddle¹⁴ found that 59,2% of patients who regularly attended the diabetes clinic at Baragwanath Hospital were insulin requiring, confirming other reports of a high proportion of insulin-treated patients attending diabetes clinics in Africa. After randomisation of their patients into a young group (age of onset of diabetes < 30 years) and an older group (age of onset \geq 30 years) and after C-peptide measurement, the authors concluded that the older group of insulin-treated patients most likely had Type 2 or non-insulin-dependent diabetes. After recalculation of their data it seems that 16% of patients attending the Baragwanath diabetes clinic are possibly true insulin-dependent patients. Of the patients presenting to the diabetes clinic at Pelonomi Hospital for the first time, 21,3% were insulin dependent as judged by the necessity to start insulin treatment within the first month after the diagnosis of diabetes.¹⁵

The clinical characteristics of IDDM patients attending diabetes clinics at a number of centres have been described. Asmal, *et al.*¹³ analysed the data for 52 black and 38 Indian patients with IDDM. The mean age at onset of diabetes was 21,8 years in black and 17,4 years in Indian patients. Six black patients had diabetes diagnosed before the age of 10 years. One hundred and ten young African and 101 young Indian patients with age of onset under 35 years were also studied by Omar and Asmal¹⁶ to determine the types of diabetes in these groups. Of the former, 86 were considered to have IDDM and 18 NIDDM, whereas of the latter the distribution was 40 and 60 respectively. IDDM tended to start at an earlier age in Indians (mean age 17 years) compared with Africans (mean age 23 years). Gill and Huddle¹⁷ observed that diabetes was rare before the age of 10 years in a group of 475 African patients attending the Baragwanath diabetes clinic. In a comparative study Kalk, *et al.*¹⁸ reported that the peak age of onset of IDDM in blacks was 22 - 23 years compared with white IDDM patients in whom the peak age of onset was 12 - 13 years. Diabetes was diagnosed in childhood in only 7% of the black patients. The reasons for the observed age differences in Africans were not clear.

The usual mode of presentation of patients with IDDM in the study of Asmal, *et al.*¹³ was acute with severe symptoms while 15% presented with keto-acidosis. In this study a positive family history of diabetes was obtained from 2 in 36 black and 16 in 25 Indian patients.

Omar and Asmal¹⁹ reported on the C-peptide response to glucagon in 25 black and 10 Indian patients with IDDM and compared it with a group of control subjects. The patients were classified as having IDDM on grounds of their dependence on insulin for control of symptoms and prevention of ketosis. Mean C-peptide levels were significantly lower in subjects with diabetes than in controls. All but 7 patients had a significant response to intravenous glucagon. Black patients as a group had lower basal and stimulated C-peptide levels compared with the Indian subjects.

Omar, *et al.*²⁰ investigated the presence of islet cell antibodies (ICA) in 47 black and 34 Indian patients with IDDM. Islet cell antibodies were present in 36% and 33% of patients respectively although the mean duration of IDDM was twice as long in black patients compared with Indian patients (6,1 years vs. 3,5 years). The findings in this study support the contention that immunological mechanisms similar to those in Caucasians play a part in the pathogenesis of IDDM in other ethnic groups.

In their study, Asmal, *et al.*¹³ observed that the mean daily dose of insulin in black patients was 76,7 U (range 22 - 580) and in Indian patients 68 U (range 20 - 170). In general, control was less than satisfactory, mainly attributed to the poor socio-economic status of most patients. Gill and Huddle¹⁷ also commented on the relatively high doses of insulin required by their African patients.

Little is known about the complications of diabetes in patients with IDDM. In Gill and Huddle's study¹⁷ the duration of diabetes was short implicating either a poor outcome or migration of patients. They found that cataract was the main complication while ischaemic heart disease was extremely rare.

In a pilot study of 39 white IDDM subjects (age range 14 - 32 years) Kalk and associates²¹ found that only a small minority consumed the recommended quantities of the three basic sources of energy. Despite routine conventional dietary advice, more than half these patients consumed less carbohydrate, and nearly 70% consumed more fat than recommended. Only 5 subjects ate an 'ideal, prudent' diabetic diet. A much freer intake of unrefined carbohydrates was recommended to make it easier for diabetes patients to restrict their fat and protein consumption.

Segal, *et al.*²² noted in healthy blacks that the glycaemic index of maize, their staple food, is significantly higher than that of bread. They advocated that refined maize should be replaced by other cereals in the dietary management of these black patients.

Elsewhere in Africa, IDDM is also not as infrequent as was previously believed. In a survey of 42 981 schoolchildren aged 7 - 14 years in Khartoum, Sudan, Elamin, *et al.*²³ found the crude prevalence of IDDM to be 0,95/1000. This is the only reported study from Africa employing WHO guidelines to determine the prevalence of IDDM. McLarty²⁴ reported from Dar es Salaam that 21,8% of diabetes patients attending the Muhimbili Medical Center required insulin for adequate control, indicating that at least some of their patients must have true IDDM.

It is clear that IDDM in black patients is not as rare in South Africa as was previously thought. IDDM in the Indian population is still a relatively rare condition. Unfortunately, little is known about the prevalence of IDDM in the white and coloured communities of South Africa. Although IDDM is not a chronic disease of lifestyle (CDL), it is an important non-communicable disease, having many features in common with NIDDM. These are clearly large gaps in our knowledge of the epidemiology of IDDM in South Africa.

THE PREVALENCE OF NON-INSULIN-DEPENDENT DIABETES MELLITUS (NIDDM) IN SOUTH AFRICAN BLACKS

Early studies

Early surveys to determine the prevalence of diabetes in this country were entirely hospital-based. The methodology was poorly described, sampling inconsistent, and the results inevitably biased. Consequently the prevalences reported merely represented an approximation of the true prevalence of diabetes in the communities studied (Table II).

Table II. The prevalence of NIDDM in South African blacks

EARLY STUDIES					
				Prevalence	
Area	Study population	Sample size	Method	Diabetes	Reference
Soweto	Outpatients (≥ 30 yrs)	2122	Urine	1,27	Seftel ²⁶
Lesotho	Outpatients (≥ 10 yrs)	3000	Urine	0,23	Politzer ²⁶
Johannesburg	(Rural) Outpatients (≥ 10 yrs)	3121	Urine	0,6	Politzer ²⁶
Guguletu (Cape Town)	Community (≥ 10 yrs)	822	Urine/Blood	2,7	Goldberg ²⁷
Mamelodi (Pretoria)	Community (≥ 10 yrs)	2015	Urine	2,9	Goldberg ²⁷

In the era prior to the establishment of the WHO criteria for the diagnosis of diabetes, the late Prof. Jackson's group from Cape Town performed the only population-based studies examining the

prevalence of diabetes in the black communities.²⁷ In their Guguletu study, the crude prevalence of diabetes was 2,7% and no age or sex standardisation to the population was calculated. Peculiarly, in this study, the highest prevalence of discovered diabetes occurred in middle-aged subjects and not in the elderly group as expected. The fact that only 7,4% of the study population was older than 55 years, may possibly explain the relative absence of elderly diabetes patients.²⁸

Recent studies

Walker²⁹ predicted that increasing urbanisation and a rise in the socio-economic status of blacks would increase their proneness to obesity, hypertension, diabetes and strokes. The prediction for diabetes was borne out by several studies performed after the 1980 and 1985 WHO criteria became established.

Seedat and co-workers³⁰ studied the prevalence of coronary heart disease risk factors in 458 black patients (age range 16 - 69 years) attending a dental clinic at King George V Hospital in Durban. Fasting serum glucose levels $\geq 7,8$ mmol/l were present in 4,9% and 3,9% of male and female subjects respectively.

Using the 1985 WHO criteria, the prevalence of diabetes has been comprehensively studied in the black population (Table III). Omar and associates³¹ studied the prevalence of diabetes in Zulus living in Umlazi, a township on the outskirts of Durban. Using a cluster sampling technique, 238 households were selected. A total of 479 subjects (141 men and 338 women) ≥ 15 years, participated in the study. The response rate was 78%. The crude prevalence of diabetes was 4,2% (women 5,2% and men 2,3%) and the overall age- and sex-adjusted prevalence 5,3%. The crude prevalence of IGT was 6,9% (women 5,5% and men 11,5%) and the age- and sex-adjusted prevalence of IGT 7,7%. The authors speculated that a rising BMI and obesity may constitute important risk factors in the emergence of diabetes in women.

Levitt and co-workers³² studied the prevalence of non-insulin-dependent diabetes mellitus and associated risk factors in urban Africans in the greater Cape Town area. The sampling frame comprised 1 000 subjects ≥ 30 years, selected with a three-stage, proportional, stratified, random cluster method. The analysis was based on 729 subjects reflecting a response rate of 79%. The crude prevalence of diabetes was 6,3% and of IGT, 5,9%. When age-adjusted to the world population, the prevalence was 8,0% (CI 5,8-10,3%) for diabetes and 7,0% (CI 4,9-9,1%) for IGT. The prevalence of diabetes among participants 30 - 65 years of age, age-adjusted to the world population, was 6,9% (CI 4,7-9,1%); in men it was 6,1% (CI 4,4-7,9%) and in women 7,4% (CI 4,6-10,1%). Similarly, the prevalence of IGT in the 30 - 65-year age group was 7% (CI 4,6-9,3%). The crude prevalence of diabetes was similar in men (6,5%) and women (6,4%). The mean age of those with diabetes was 56 ± 12 years, compared with 44 ± 13 years in the non-diabetes participants. Of the 46 diabetes subjects, 24 had been diagnosed previously of whom only 16 (66%) were seeing a medical practitioner or attending a clinic for their diabetes.

In this study, logistic regression analysis identified the following factors as independent risk factors for diabetes: age (odds ratio 4,18 (95% CI 2,48-9,52)), upper segment body fat distribution (odds ratio 2,94 (95% CI 1,47-5,64)), urbanisation i.e. more than 40% of life spent in an urban area (odds ratio 2,32 (95% CI 1,09-4,95)), and obesity (odds ratio 2,31 (95% CI 1,06-5,02)).³² The selected model did not indicate sex, physical activity, alcohol intake, or a family history of non-insulin-dependent diabetes, as risk factors. Interestingly, multivariate analysis indicated that age was the only independent predictor of IGT in this survey (odds ratio 4,06 (95% CI 2,06-6,06)).

The prevalence of diabetes was also determined in an urban Free State black population (Mangaung), and compared with that of the partly rural population of QwaQwa.³³ From Mangaung 741 subjects (284 male and 457 female) and from QwaQwa 853 subjects (279 male and 574 female) ≥ 25 years, participated in the study. A standard 75g OGTT was performed and results interpreted by the 1985 WHO criteria. The age- and sex-adjusted prevalence of diabetes was 6%

and 4,8% for Mangaung and QwaQwa respectively. The prevalence of IGT was 12,2% and 10,7% respectively. A BMI of ≥ 25 was associated with abnormal glucose tolerance in the Mangaung sample (relative risk 1,9, 95% CI 1,4 - 2,5) whereas the relationship was not statistically significant in the QwaQwa sample. Central obesity, however, was significantly associated with glucose intolerance in both samples: the relative risk was 2,8 (95% CI 2,0 - 3,8) for the Mangaung sample and 2,3 (95% CI 1,7 - 3,2) for the QwaQwa sample. Also, in both samples more treated than untreated hypertensives had diabetes (19% vs. 9,4% and 16,8% vs. 5% for Mangaung and QwaQwa respectively). The advanced stage of westernisation of this rural population is emphasised by these data.

Table III. The prevalence of NIDDM in South African blacks

STUDIES USING WHO CRITERIA						
Area	Study population	Sample size	Method	Prevalence		Reference
				Diabetes	IGT	
Mangaung (Bloemfontein)	Community (≥ 25 yrs)	741	Blood	6,0*	12,2*	Mollentze ³³
QwaQwa (Orange Free State)	Community (≥ 25 yrs)	853	Blood	4,8*	10,7*	Mollentze ³³
Cape Town	Community (≥ 65 yrs)	729	Blood	8,0*	7,0*	Levitt ³²
Umlazi (Durban)	Community (≥ 15 yrs)	479	Blood	5,3*	7,7*	Omar ³¹

* Age adjusted

These recent studies indicate that the prevalence of diabetes is considerably higher in African subjects than ± 25 years ago²⁷ but differences in methodology render it difficult to determine whether the prevalence of diabetes has actually increased. Should this be so, the degree of obesity and level of urbanisation are possible factors which may contribute to the rise in prevalence. It is clear, however, that diabetes was much more common in the South African black population than in Tanzanian subjects. Longitudinal studies would be required to resolve this issue as well as to expand on the possible risk factors for the development of IGT and diabetes in this population.

IN AFRICA

The Tanzanian study³⁴ was the first epidemiological study based on the 1985 WHO criteria to determine the prevalence of diabetes in Africans. In this study 6 097 rural subjects aged 15 years and older (mean age 37 years) in 6 villages were examined. The overall prevalence of diabetes in this study was 0,87% and that of IGT 7,7%. Of the 53 diabetes patients 7 were previously known to be so and 46 were newly diagnosed, of whom only 12 had symptoms of hyperglycaemia. The male:female ratio for diabetes was 1,2:1 and did not differ from that in the study population. Multiple regression analysis showed that fasting blood glucose was positively related to systolic blood pressure and negatively to BMI, smoking, drinking, and haemoglobin. The 2-hour blood glucose was related positively to age, systolic blood pressure, and female sex and negatively to BMI, haemoglobin, and smoking. Fasting blood glucose levels were not associated with increasing age although 2-hour blood glucose levels were associated to a small degree with increasing age. From this the authors concluded that for most of the population glucose tolerance did not deteriorate with age. Whether this phenomenon holds true for urban subjects remains to be seen.

The prevalence of diabetes in different African and US populations where a 75 g OGTT was used to diagnose diabetes, is shown in Table IV. Keeping differences in sampling frames and procedures

in mind, diabetes was notably more common in the South African populations with prevalence rates approaching that of US blacks. It is of considerable interest to note the North-South gradient in the prevalence of diabetes. The same observation was also made for hypertension and obesity pointing towards the possible role of affluence in the pathogenesis of CDL.

The importance of IGT in African subjects still awaits clarification and the question of whether IGT in African subjects is also associated with an increased risk of diabetes, still has to be addressed.

After examining available data, McLarty²⁴ was sceptical that the prevalence of diabetes was on the increase in Sub-Saharan Africa. He was also not convinced of any real difference in the prevalence of diabetes between urban and rural areas, quoting Politzer and Schneider's work.²⁶ The number of NIDDM on the African continent was estimated to be at least 1 million based on a total population of 555 million.²⁴

Table IV. Prevalence of diabetes mellitus in Africa and the USA using WHO Criteria

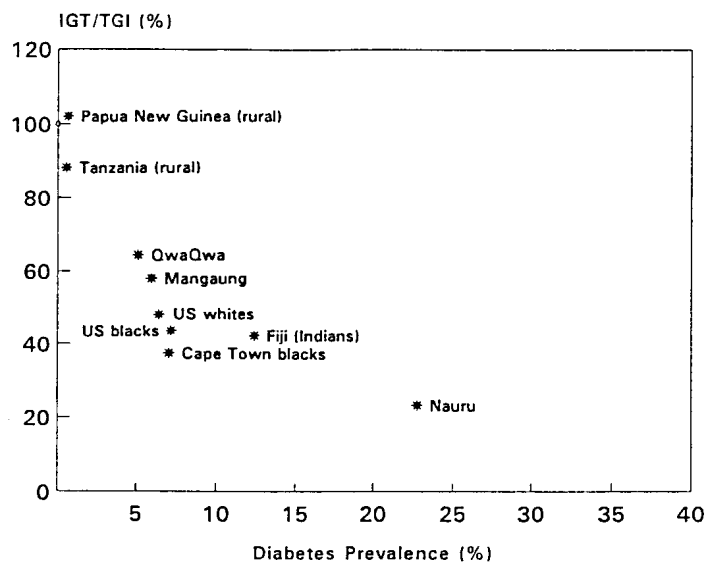
Country	Age group (years)	Prevalence %	Reference
Tanzania (rural)	15 +	0,9	McLarty ³⁴
Tanzania (rural and urban)	All	0,7	Ahren ³⁶
Mali (rural)	15 +	0,9	Fisch ³⁶
QwaQwa (semi-rural)	25 +	4,8	Mollentze ³³
Mangaung (urban)	25 +	6,0	Mollentze ³³
Cape Town (urban)	30 +	8,0	Levitt ³²
USA	20-74	whites 6,4 blacks 9,9	Harris ³⁷

Dowse, *et al.*³⁸ suggested that an index such as the ratio of IGT to total glucose intolerance (TGI) may serve as an indicator of the 'epidemicity' or potentiality for NIDDM to increase in incidence and prevalence in a population. This interesting hypothesis was based on the recently observed decline in the prevalence and incidence of IGT and the stabilisation in the prevalence and incidence of NIDDM in Nauruans.³⁸ It has also been previously shown that subjects with IGT are at increased risk of developing diabetes.⁶ The IGT/TGI (total glucose intolerance) index may serve as a rough public health indicator of a population's susceptibility to a higher NIDDM prevalence.

The IGT to TGI ratios for a number of populations are plotted against their diabetes prevalence rates which are adjusted to the standard world population (Fig. 1). A high prevalence of IGT in the presence of a low diabetes prevalence (a high IGT/TGI ratio) may indicate an early stage of a diabetes epidemic, e.g. rural blacks in Tanzania. Some populations like blacks and Hispanics in the USA, demonstrated a high prevalence for both IGT and diabetes. This may suggest that a serious existing situation may deteriorate further. In the Pima Indians as well as the Nauruans the prevalence of diabetes was about half that of the IGT prevalence, suggesting that the epidemic of diabetes may already be waning in these populations, or alternatively, that the most genetically susceptible persons already manifest the disease fully.

This interesting concept of an epidemicity index deserves to be examined further in longitudinal studies in this country. It is obvious that diabetes is no longer confined to developed nations but is already a problem of the developing Third World nations. For far too long have diabetes and abnormalities of glucose tolerance been neglected in South Africa. More information is urgently

needed for all ethnic groups in order to plan future health services for the country.



(Adapted from Dowse, *et al.* 1989)

Figure 1. IGT as a proportion of total glucose intolerance versus prevalence of diabetes mellitus

THE PREVALENCE OF DIABETES IN SOUTH AFRICAN INDIANS

Early studies

Cosnett^{39,40} first drew attention to the high prevalence of diabetes mellitus among Indian patients admitted to the King Edward VIII Hospital in Durban. Diabetes accounted for more Indian patients being admitted to the medical wards than any other single disease. Cosnett also emphasised the rarity of ketosis among Natal Indians.⁴⁰ The high prevalence of diabetes mellitus in the Natal migrant Indian community subsequently became the focus of much interest. (Table V).

Table V. The prevalence of NIDDM in South African Indians

EARLY STUDIES					
Area	Study population	Sample size	Method	Prevalence %	
				Diabetes	Reference
Springfield (Durban)	Community (≥ 20 yrs)	223	Urine	5,5	Wood ⁴¹
Tongaat (KwaZulu Natal)	Community (≥ 10 yrs)	1619	Urine	7,2*	Campbell ⁴²
Tongaat (KwaZulu Natal)	Mill Barracks (≥ 10 yrs)	3354	Urine	3,3*	Campbell ⁴²
Cape Town	Community (≥ 10 yrs)	1123	Urine/Blood	4,3 - 6,0	Marine ²⁸
Tongaat (KwaZulu Natal)	Community (≥ 10 yrs)	2427	Urine/Blood	6,0 (13,0*)	Jackson ¹¹

* Age adjusted

Campbell identified a subgroup within Cosnett's series as being 'insulin-independent young diabetics'.⁴³ This type of diabetes has not been recognised by the WHO as a separate subgroup. In a later study, Jialal, *et al.*⁴⁴ reported on the clinical characteristics of 85 Indian patients believed to belong to this subgroup which he called NIDDDY (non-insulin-dependent diabetes in the young). The inclusion criteria were as follows: age of onset under 35 years; duration of diabetes greater than 1 year; aketonuric but symptomatic presentation; prevention of ketonuria and satisfactory control of symptoms without insulin therapy. In addition, the WHO (1980) criteria for the biochemical diagnosis of diabetes also had to be satisfied. The most remarkable clinical feature was the familial aggregation of the disorder. A positive family history was present in no less than 82% of the patients: 75% of patients had a parent and 41% a sibling with diabetes. Another characteristic of the group was the fasting hyperinsulinaemia with a delayed and attenuated insulin response. With respect to their insulin response to a glucose load, there were no significant differences between obese and non-obese NIDDDY patients, signifying that obesity does not exert a significant modulating effect on their insulin secretion.⁴⁵

Recent studies

Omar and colleagues conducted the first survey among South African Indians based on WHO criteria (1980).⁴⁶ Employing a cluster sampling method, 866 subjects 15 years and older from a low socio-economic area (Chatsworth) in Durban were studied. The crude prevalence of diabetes was 11% and that of IGT was 5,8%. Previously diagnosed cases accounted for 50% of those with diabetes. In this study diabetes was more common in women (13,5%) than in men (7,6%). However, IGT was more common in men (7,1%) than in women (4,8%). The insulin-dependent form of diabetes mellitus was found in only three subjects. The frequency of both diabetes and IGT rose with age. Over the age of 30 years 30,6% had some abnormality of glucose tolerance (diabetes 21,7%, IGT 8,9%) while in those over 40 years, the corresponding figure was 38,9% (diabetes 26,9% and IGT 12%). Although both diabetes and IGT were more common in obese than non-obese subjects, there was no correlation between the BMI and the fasting or 2-hour plasma glucose levels. Apart from age, no other risk factor for diabetes or IGT emerged from this study. Comparing their data with those of Marine,²⁸ Omar and colleagues concluded that over the previous 15 years the prevalence of diabetes and IGT has increased by about 50%.

Table VI. The prevalence of NIDDM in South African Indians

STUDIES USING WHO CRITERIA						
				Prevalence (%)		
Area	Study population	Sample size	Method	Diabetes	IGT	Reference
Chatsworth (Durban)	Community (15 yrs)	866	Blood	11,0	5,8	Omar ⁴⁶
Durban	Community (15 yrs)	2479	Blood	13,0*	6,9*	Omar ¹²

* Age adjusted

Recently Omar and associates reported the results of a large study to determine the prevalence of diabetes and the possibility of a bimodal distribution of plasma glucose levels in the Durban Indian population.¹² Subjects were selected by systematic cluster sampling of households and a modified OGTT performed on 2479 Indian subjects > 15 years of age. The overall response rate in terms of households was 82% and in terms of potentially eligible subjects it was 92%. The age- and sex-adjusted prevalence of diabetes was 13% (women 15% and men 10,4%). The age- and sex-adjusted prevalence of IGT was 6,9% (women 5,8%, men 8,9%). The relatively few cases (25%) of newly diagnosed diabetes in this study is probably an indication of the level of awareness of diabetes in this ethnic group. No difference in the prevalence of diabetes was found in terms of

socio-economic area or home language. Both NIDDM and IGT was associated with increasing age. More than 30% of subjects who were 35 years and over had some abnormality in glucose tolerance, 20% had diabetes mellitus and 10,6% IGT. Obesity, which was commonly observed in the diabetes subjects, was considered to be a pathogenetic factor. Obese diabetes subjects had a stronger family history of a first-degree relative with the disease (67,1%) compared with obese subjects without NIDDM (31%), suggesting an interplay between genetic factors and obesity in unmasking the diabetes state in this group. In keeping with other population groups with a high prevalence of NIDDM, South African Indians also show a lower prevalence of IGT compared with NIDDM, thereby suggesting bimodality in the 2-hour plasma glucose response to a glucose load. In this study bimodality in both fasting and 2-hour plasma glucose distribution could be shown for both sexes in the 55 to 74-year age group, suggesting that at-risk subjects in this population may move fairly rapidly from normal glucose tolerance to NIDDM. The biological mechanism of the bimodality phenomenon is poorly understood.

Motala, *et al.*⁴⁷ examined the natural history of IGT in 128 Natal Indians over a 4-year period. She found that 50,4% of subjects (12,6% per year) progressed to NIDDM - a strikingly high risk compared to other populations characterised by a high prevalence of diabetes such as the Pima Indians and Nauruans. Remarkable also was that the majority (72%) who progressed to NIDDM did so in the first year. IGT persisted in 24,8% of subjects while 24,8% reverted to normal glucose tolerance. The most significant predictor of subsequent NIDDM was the baseline blood glucose concentration - both fasting and after two hours. In this study the risk of progression to NIDDM was total if the baseline 2-hour plasma glucose was $\geq 10,2$ mmol/l or if the baseline fasting plasma glucose $\geq 7,3$ mmol/l. BMI and gender failed to emerge as significant predictors in multivariate analysis in this group. Furthermore, measures of insulin resistance and pancreatic secretory defect also did not appear to play a role in the risk of progression to NIDDM.

IN WHITE SOUTH AFRICANS

The only survey describing the prevalence of diabetes among white South Africans, was reported by Jackson and co-workers in 1969.⁴⁸ A representative sample consisting of 1 186 persons over the age of 10 years were screened. The age-adjusted prevalence of diabetes in subjects 15 years and older was 3,7% according to criteria, which were more stringent than the 1985 WHO criteria. The diabetes rates were very similar for Afrikaans- and English-speaking subjects but slightly higher for Jewish subjects. The authors observed that obesity was more common among diabetes than non-diabetes patients. However, fewer diabetes patients volunteered a positive family history of diabetes than those in other European surveys.

IN COLOURED

The late Professor Jackson's group also studied the prevalence of diabetes in 968 subjects representative of the Cape coloured community.⁴⁹ The crude as well as age-adjusted prevalence of diabetes in those over the age of 15 was 8,7%. Obesity was 'clearly related' to diabetes and was more common in females, although the rates of diabetes were the same for both genders. Interestingly, 7 discovered diabetes patients were under 20 years of age and none were ketotic. Evidence of ischaemic heart disease was found in 11 of these 41 discovered patients and hypertension in 12.

GESTATIONAL DIABETES

The importance of gestational diabetes, defined as diabetes with first recognition or onset during pregnancy, rests in its association with increased perinatal losses, risk of fetal macrosomia, birth trauma, operative delivery and more frequent morbidities, i.e. hypoglycaemia, hypocalcaemia, polycythaemia and hyperbilirubinemia. In addition, in the long-term there is an increased risk of NIDDM in the mother and possible obesity in the offspring. The recognition of gestational diabetes is a problem as it is almost always asymptomatic and selective screening for glucose intolerance

on the basis of risk factors may not identify up to one half of patients. The major public health issues of gestational diabetes therefore relate to its diagnosis, pathogenesis and management.

The prevalence of gestational diabetes in this country is largely unknown. No study has been conducted in the black or white populations. Ranchod, *et al.*⁵⁰ studied the prevalence of gestational diabetes in the patient population drawn from the large Indian and small coloured communities from the Pietermaritzburg area who attended the antenatal clinic at Northdale Hospital over a 1-year period in 1987 - 1988. The subjects were screened at booking and again at 28 - 32 weeks gestation, using a 75 g OGTT. If the one-hour venous plasma glucose was $\geq 7,8$ mmol/l, a formal 75 g OGTT was performed and gestational diabetes diagnosed if the 2-hour venous plasma glucose was $\geq 7,8$ mmol/l. Screening was conducted in 1 717 patients by 32 weeks, of whom 17,2% required a formal OGTT. The prevalence of gestational diabetes was 3,8%, is lower than might be expected in the Indian community with its high reported prevalence of NIDDM, and who comprised the majority of the study population.^{12,43}

Jackson and Coetzee⁵¹ determined the prevalence of gestational diabetes in patients attending the Groote Schuur Hospital antenatal clinic who had one of the number of indications warranting an oral glucose tolerance test. These included a family history of diabetes in a parent or sibling, repeated miscarriages, a weight of greater than 80 kg, a previous infant weighing more than 4 000 g, previous perinatal death, previous infant with severe congenital anomaly, Indian origin, fasting or repeated glucosuria, polyhydramnios and previous hyperglycaemia. They utilised a 50 g OGTT. Diabetes was diagnosed when two of the following three values were exceeded: fasting $> 5,5$ mmol/l, maximum (excluding 30-minute figure) of > 10 mmol/l and a 2-hour $> 6,7$ mmol/l. In the study, 3 783 patients were screened, 588 received an OGTT which was abnormal in 3%. Their conclusions were that glucose tolerance testing should be restricted to those with either random or fasting glucosuria, two or more of the abovementioned indications and a report of previous hyperglycaemia.

The impact of appropriate management of gestational diabetes on fetal outcome in this country has been reported. Coetzee and Jackson found that the overall perinatal mortality in treated patients was 10 per thousand, compared with a peri-natal mortality of 140 per thousand in untreated patients.⁵¹ More recently, Huddle, *et al.*⁵² from Baragwanath Hospital reported that patients with gestational diabetes who received intensive therapy, had a perinatal mortality rate of 4,7% compared with that of 21,4% in those who had booked too late to receive more than two weeks of intensive therapy before delivery. The stillbirth (4% vs. 21,4%) and early neonatal deaths (0,7 vs. 2,7%) were considerably higher in the untreated groups, but the congenital abnormality rates were similar (1,3% vs. 0,9%).

It is clearly important to diagnose and treat gestational diabetes. None the less, the relatively low reported prevalence of 3% in a largely Indian population in whom the highest reported prevalence of NIDDM (non-pregnant) is found in this country, would suggest that further studies of the prevalence of gestational diabetes are not a priority.

RISK FACTORS FOR AND PATHOGENESIS OF NIDDM

Numerous local epidemiologic as well as metabolic studies have contributed to our present knowledge of risk factors for and understanding of the pathogenesis of NIDDM, especially in the black population. Unfortunately many questions still remain unanswered.

Risk factors

Epidemiological studies, especially the more recent ones, identified various risk factors for the development of glucose intolerance. Obesity has been implicated as a risk factor in almost all studies involving the various ethnic groups in South Africa. Unfortunately no uniform definition of overweight or obesity was used and few of the studies attempted to quantify the risk imposed by

obesity.

Among Natal Indians¹² obesity was more common in subjects with NIDDM (47,1%) and IGT (57,5%) than in those with normal glucose tolerance (16,3%). Obesity was also more frequent in women with glucose intolerance than in men. Body mass index, however, did not emerge as an independent risk factor predicting the progression of IGT to NIDDM in Indians over a 4-year period.⁴⁷ The short follow-up period may have been the reason for this unexpected finding.

In black Capetonians the crude prevalence of NIDDM increased with both BMI and upper segment fat distribution.³² In this study obesity was defined as a BMI of ≥ 27 kg/m² for men and ≥ 25 kg/m² for women. In men central obesity was regarded as a waist-to-hip circumference ratio $\geq 0,92$ and in females $\geq 0,84$. In subjects with lower segment fat distribution the crude prevalence of NIDDM was 1,3% in the non-obese compared to 4,8% in the obese. In those with upper segment fat distribution the non-obese had a crude prevalence of 10,9% while in the obese the prevalence was 16,0%. This indicates an additive effect of obesity and upper segment fat distribution which was consistent in men and women. In multivariate analysis central obesity as well as obesity emerged as independent risk factors for NIDDM with odds ratios of 2,94 (95% CI 1,47 - 5,64) and 2,31 (95% CI 1,06 - 5,02) respectively. Obesity was also considered to be an important risk factor for diabetes in black women.³⁰

Age is strongly associated with both IGT and NIDDM. In Natal Indians more than 30% of the subjects, ≥ 35 years of age, had some abnormality in glucose tolerance, 20% having NIDDM and 10,6% IGT.⁴³ Eighty-five percent of the 20 black diabetes patients in the Natal study were ≥ 35 years and 66% of the 33 subjects with IGT were ≥ 35 years.³⁰ In this study both fasting and 2-hour plasma glucose levels in both sexes significantly correlated with age. In Cape Town blacks the prevalence of diabetes increased over the age deciles while only 2 patients (out of 46) were < 35 years of age.³² In this study, age emerged as the strongest risk factor for diabetes (odds ratio 4,18, 95 CI 2,48 - 9,52) while age was the only significant independent risk factor for IGT (odds ratio 4,06, 95 CI 2,06 - 6,06).

The Cape Town study was the only one which examined the relationship between urbanisation and NIDDM. Urbanisation, defined as 40% and more life spent in the city, was also an independent risk factor for NIDDM (odds ratio 2,32, 95% CI 1,09 - 4,95).³²

Importantly, the population-attributable risk fractions were also calculated in the study of black Capetonians.³² Population-attributable risk fractions for NIDDM were: 40% for urbanisation, 43% for obesity and 53% for upper segment fat distribution. Since these were independent factors, it follows that if all three risk factors were removed, this would reduce the prevalence of NIDDM from 6,3% (crude rate) to an estimated 1%. This, however, would require interventional programmes directed at reduction in obesity, upper segment fat distribution, and to a lesser degree, lifestyle changes associated with urbanisation.

Interesting but inconclusive data are available on the genetics of both NIDDM and IDDM in South African Indian and black subjects. Omar, *et al.*⁵³ reported on the frequency of a positive family history of diabetes in a group of 118 black and 125 Indian subjects who had developed diabetes before the age of 35 years. According to WHO (1980) criteria, subjects were divided into IDDM and NIDDM. Fifty-four percent of Indian patients and 12% of black patients with IDDM had a positive family history of diabetes, while 80% and 37% respectively of patients with NIDDM had a positive family history. The presence of a family history of NIDDM in almost half the Indians with IDDM was remarkable because of the relative rarity of IDDM in Indians and because NIDDM was implicated in the pathogenesis of insulin-dependent disease. Genetic heterogeneity of the disease in the first degree relatives is the only rational explanation for the findings observed in this study.

No information is available on the genetics of NIDDM in South Africans except in Natal Indians. Omar and associates¹² found that obese diabetes subjects had a stronger family history of a first

degree relative with NIDDM (67%) than obese subjects without NIDDM (31%). In contrast, only 40% of the non-obese diabetes subjects had a first degree relative with the disease. This association was interpreted as supporting the hypothesis of an interplay between genetic factors and obesity. In young South African Indians of North Indian origin a positive correlation with HLA B15 was shown while an increased frequency (but statistically insignificant) of HLA Bw61 was found in Indian NIDDM patients as a whole.⁵⁴ The frequency of HLA A2 was found to be increased in Xhosa subjects with NIDDM but this was also not significant.⁵⁵ Shires, *et al.*⁵⁶ also did not find a significant alteration in HLA A or B antigen frequencies in Johannesburg blacks with NIDDM. In their study of NIDDM presenting before 35 years in Indian and black patients, Asmal, *et al.*⁵⁷ found a positive family history of diabetes in 75% and 55% of patients respectively. Since the number of blacks in this study was only nine, the results should be interpreted with caution. In their study of Cape Town blacks, Levitt, *et al.*³² found no association between family history and NIDDM.

This was the only study in this country that also examined the relationship between physical activity and NIDDM. Only one subject who performed heavy physical activity had diabetes. Surprisingly, there was no statistically significant relationship between NIDDM and physical activity. The crude measurement of physical activity was the probable explanation for the lack of significant relationship. In this study no relationship was found between alcohol intake and NIDDM.

The pathophysiology of NIDDM

DeFronzo⁵⁸ proposed that the full-blown syndrome of Type 2 (non-insulin-dependent) diabetes mellitus requires the simultaneous presence of two defects, insulin resistance and impaired β cell function. In his review it was suggested that in the earliest stage of NIDDM, both hepatic and peripheral resistance to insulin are well established and offset by the presence of compensatory hyperinsulinaemia. Overt diabetes developing only when the pancreas is unable to meet the increased and sustained demand for insulin secretion.

Various studies were performed over the past 25 years in this country in different ethnic groups to examine β -cell function in normal and glucose-intolerant subjects. In a careful study Rubenstein, *et al.*⁵⁹ showed that fasting as well as post-glucose serum insulin levels were significantly lower in normal black than in normal white subjects, despite similar mean blood glucose levels. After studying β cell function in a group of Indian and coloured subjects, Jackson, *et al.*^{60,61} concluded that the earliest biochemical lesion in NIDDM is associated with insulin excess rather than insulin deficiency. Keller⁶² from Jackson's unit, compared fasting and post-glucose serum insulin levels in subjects from different ethnic groups and with different levels of glucose tolerance. Keller concluded that values found for Cape blacks were higher than those in the white and coloured groups, while levels for Indians were considerably higher.⁶² It was further concluded that with increasing impairment of carbohydrate metabolism, insulin levels rise, reaching a maximum in 'mild' diabetes patients, but that they become low or very low with increasing severity of the disease.

In an often cited paper, Wicks⁶³ examined the insulin response to a 50 g oral glucose load in 42 newly diagnosed black diabetes patients admitted to the Harare Hospital for stabilisation. Fasting serum insulin levels were significantly higher in the diabetes patients (21 uU/ml) than in a control group (15 uU/ml) of 50 black male cleaners of the same social and economic background. However, at 60 and 120 minutes those with diabetes secreted far less insulin than the control subjects. Wicks concluded that black diabetes (and healthy) subjects secreted far less insulin than healthy whites.⁶³ Interestingly, 76% of their diabetes subjects were considered to be 'insulin dependent'. This study has several weak points including possible biased selection of diabetics and the failure to control for sex, age and obesity in analysing the data. Furthermore, the control subjects were only males (surely leaner than females), glucose toxicity was unknown at that time (median fasting plasma glucose in those with diabetes was 12,8 mmol/l and at 60 minutes 21,4 mmol/l) and the fact that 23% of them had steatorrhoea indicated chronic pancreatitis. Their relative insulinopenia was hypothesised to explain the 'rarity of typical non-insulin dependent diabetes' and coronary heart disease in blacks.

Joffe, *et al.*⁶⁴ examined aspects of carbohydrate and lipid metabolism in 50 non-diabetes blacks of whom half were regarded as having simple obesity (weights exceeding 10% of ideal body weight). The obese subjects were characterised by significantly raised basal as well as stimulated insulin levels. The elevated insulin responses in the overweight group did not correlate with the degree of adiposity but fasting triglyceride levels were strongly correlated with both basal and stimulated insulin levels. Joffe concluded from these results that the classical sequential hypothesis of obesity-causing insulin resistance and compensatory hyperinsulinism may not apply in all environmental circumstances.⁶⁴ He hypothesised that the sequence of events might be reversed, with increased insulin secretion being an early event and obesity partly the consequence of augmented lipogenesis.

Asmal and Leary⁶⁵ carried out glucose tolerance tests on 35 recently discovered matched Indian and black NIDDM patients. Fasting as well as 2-hour post-load blood glucose levels were significantly higher in black females compared with Indian females. The insulin response in the black group was attenuated with a peak value at 60 minutes of only 22uU/ml compared with a corresponding value of 40 uU/ml in the Indian group.

Shires, *et al.*⁶⁶ studied the insulin response to a glucose load in four groups of subjects: i) obese 'chemical diabetics' (including some individuals with IGT); ii) obese symptomatic but untreated diabetes individuals; iii) non-diabetes non-obese males; and, iv) non-diabetes obese females. They found a relatively low insulin response to glucose in the normal males. Severe insulinopenia was observed in the obese symptomatic diabetes subjects. The obese non-diabetes females had a significantly greater insulin response at all times during the OGTT except at 60 minutes compared with the non-obese male subjects. The authors concluded from these data that obesity causes insulin resistance and hyperinsulinaemia, followed by a progressive decline in insulin secretion with increasing glucose intolerance eventually leading to β -cell exhaustion in blacks with diabetes.

In a subsequent study Shires, *et al.*⁶⁷ investigated and compared the β -cell response to a glucose challenge followed by intravenous glucagon and tolbutamide (maximal β -cell stimulation) in a group of obese black and white females. The basal insulin levels in the black group were significantly lower compared with the white group. (Interestingly, the mean fasting insulin levels of the obese blacks in this study were only about half that of the obese black females in their earlier study although they were equally obese). The black group also had significantly lower insulin levels at 30 and at 60 minutes post challenge. Basal as well as 30- and 60-minute C-peptide levels were also significantly lower in the black subjects. The authors concluded that the β -cell secretory capacity of black obese subjects was less than that of white obese subjects.

A Johannesburg group⁶⁸ also examined and compared insulin receptor binding characteristics in four groups of ten black women: a young non-obese non-diabetes group (A); a middle-aged, non-obese, non-diabetes group (B); a middle-aged, obese, non-diabetes group (C); and a middle-aged, obese group of newly diagnosed but untreated diabetes patients (D). They found that specific insulin binding as well as total receptor concentration decreased significantly from group A through group B and C to group D. Receptor concentrations correlated inversely with fasting plasma glucose, insulin, free fatty acids, and body mass index, suggesting a dependence on these metabolic variables leading to receptor down regulation. It was concluded that NIDDM appeared to be preceded by a progressive decline in receptor concentration in middle-aged, obese, non-diabetes individuals in whom fasting hyperinsulinaemia may have led to the downregulation of insulin receptors.

Using the euglycaemic insulin clamp technique, Wing, *et al.*⁶⁹ showed that glucose utilisation was appreciably reduced in obese, black patients with untreated NIDDM. This abnormality normalised following sulphonylurea treatment and was accompanied by an increase in insulin receptor concentration but not with changes in basal insulin secretion as determined from C-peptide measurements.

These studies urged Joffe and co-workers⁷⁰ to propose an alternative hypothesis for the

pathogenesis of NIDDM in black South Africans (Fig. 2). This concept is also partly based on the Hales and Barker hypothesis,⁷¹ which proposes that one of the major long-term consequences of inadequate early nutrition is impaired development of the endocrine pancreas and a greatly increased susceptibility to the development of NIDDM. As was eloquently outlined by Joffe and Seftel⁷² their hypothesis has important therapeutic implications. It was predicted that the therapeutic response to oral sulphonylureas will be rather brief in black patients with NIDDM before secondary failure develops. This has, however, yet to be proved in prospective studies. The frequent need for permanent or intermittent insulin therapy in these patients has also been mentioned.

Although pancreatic iron overload as part of Bantu siderosis has become rare as a cause of diabetes the contribution of chronic alcoholic pancreatitis to the overall incidence of diabetes among black South Africans is unknown.⁷²

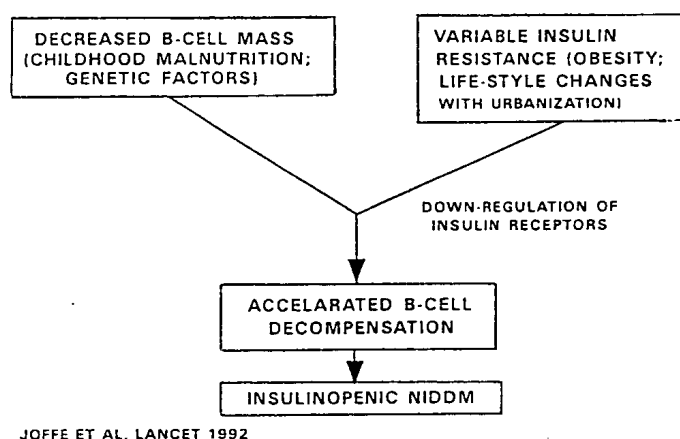


Figure 2. Proposed scheme for the pathogenesis of NIDDM in the black population of southern Africa⁷⁰

COMPLICATIONS OF DIABETES MELLITUS

The major threat to life and health of those afflicted with diabetes is progressive damage to the eyes, kidneys, nerves and arteries which, unfortunately, result in early disability and death.⁷³ In developed countries the complications of NIDDM present a public health problem greater than that of any infectious disease⁷⁴ and most diabetes patients in these countries will die of a condition related to it;⁷⁵ 60% of deaths in a diabetes cohort were due to vascular disease (coronary heart disease 35%, cerebrovascular disease 22% and general atherosclerosis, including gangrene 3%). Besides coronary events there is strong evidence that congestive heart failure without significant atherosclerosis occurs more frequently in diabetes patients than in the general population.⁷⁵ It is important to bear in mind that worsening glucose tolerance and hyperinsulinaemia are frequently an integral part of a cluster of cardiovascular risk factors^{76,77}

According to the Central Statistical Services⁷⁸ diabetes was responsible for 2,8% of total mortality in blacks 25 years and older, during 1990 in South Africa. In this age group diabetes was the registered cause of death in 709 men (1,9%) and 1 098 women (4,1%). Seventy-four deaths below the age of 25 years were attributed to diabetes.

The causes of mortality in NIDDM are summarised in Table VII. Overall mortality in NIDDM is increased two-three fold and life expectancy is reduced by 5 - 10 years compared with the general population.¹

The clinical epidemiology of the complications of diabetes has been inadequately studied in South Africa. Remarkably few comprehensive local studies focused on the frequency of macro- and microvascular complications.

Table VII. Causes of Mortality in Non-insulin-dependent diabetes

	%
Cardiovascular disease	58
Cerebrovascular disease	12
Nephropathy	3
Diabetes coma	1
Malignancy	11
Infections	4
Other	11

Marks and Kraal, 1971¹

Acute metabolic complications

It is to be expected that in a developing country, clinicians will focus their attention on the acute metabolic complications of diabetes, since these may have grave consequences for the patients. Studies on both hypoglycaemic and hyperglycaemic emergencies have been reported by clinicians from Baragwanath Hospital.

An analysis of the large number of hyperglycaemic emergencies admitted to this hospital revealed that many could have been prevented.⁷⁹ During an eight-week study, 60 patients who complied with the definition of a hyperglycaemic emergency (a patient admitted to hospital and who received intravenous insulin and fluids) were admitted. Fifteen (25%) of these patients died in hospital. Only three deaths may have been unrelated to the hyperglycaemic emergency. Another 3 patients died within 3 months after discharge. Patients were also at high risk of readmission: One third of those discharged being readmitted within 3 months. The authors estimated that the treatment of hyperglycaemic emergencies cost the Soweto health services at least R462 000,00 in 1981. Poor compliance and ignoring of significant symptoms contributed to these hyperglycaemic emergencies. In addition, factors for which the health service should bear responsibility, including the failure to issue diabetes identification bracelets and ensuring that patients have the necessary skills and knowledge, were also identified as contributory causes. A plea was made for the upgrading of ambulatory diabetes services, which have led to significant savings and reductions in diabetes coma admissions elsewhere in the world.

Exactly 5 years later Huddle and Gill⁸⁰ repeated their study over a similar two-month period after a programme of improved diabetes management was embarked upon. The number of admissions declined from 60 to 48 and the mortality rate from 25% to 10%. Four of the five deaths were due to strokes. This study showed that considerable improvements can be made in both prevalence and mortality of hyperglycaemic emergencies in a Third World setting.

Hypoglycaemia was also identified as a significant problem, accounting for 6% of diabetes admissions over a five-month period in Baragwanath Hospital.⁸¹ Contributory factors to severe hypoglycaemia were the omission of food, alcohol excess, gastrointestinal upset and inappropriate treatment. Sulphonylureas contributed to one third of episodes. There was no mortality and long-term morbidity. Patient education, particularly with regard to regularity of food intake, avoidance of alcohol excess, and the self-management of intercurrent gastrointestinal illness were identified as areas in need of improvement.

Microvascular and other diabetes-related complications

Diabetes accounts for approximately 25% of all patients with end-stage renal disease in the United States.⁸² Analyses of the data in the Michigan Kidney Registry indicated that the incidence of diabetes end-stage renal disease was 2,6 fold higher among blacks than whites after adjusting for the higher prevalence of diabetes among the former. A possible explanation for the findings in this study may have been the higher mean diastolic blood pressure of black patients (92,6 mmHg vs. 88,2 mmHg for white patients) before the onset of end-stage renal disease.

The incidence and prevalence of diabetes nephropathy and diabetes end-stage renal disease in black South Africans with NIDDM, is unknown. It is, however, a matter of great concern for clinicians particularly in view of the increasing numbers of NIDDM patients.

The situation with regard to the number of diabetes patients with end-stage renal disease on chronic dialysis programs in South Africa, is quite different from the USA situation. Diabetes was not mentioned as a cause of end-stage renal disease in 1 131 patients registered by the South African Dialysis and Transplant Registry.⁸³ This paper highlighted great disparity in the racial distribution of dialysis patients in Natal where 22 per million of the population received chronic dialysis. Of these, 2 per million were black, 20 per million coloured, 55 per million Indian and 59 per million white; this against the background of blacks comprising 78% of the population of Natal. The most important reason for this disparity was the divergence of the socio-economic status of the groups. In addition, at the Johannesburg Hospital diabetes patients are only rarely accepted for chronic dialysis (Prof. A Meyers personal communication, 1992).

Among 207 Natal Indians with diabetes admitted to hospital for various reasons, 10,6% were ketotic.⁴⁰ Infections including skin, urinary tract and respiratory infections were noted in 45%, while retinopathy, albuminuria and neuropathy was present in 27%, 16% and 19% of admissions respectively. Cataracts were observed in 12% of patients. Jackson⁸⁴ reported diabetes retinopathy in 61%, proteinuria in 21% and peripheral neuropathy in 38% of a group of 134 Indians at a diabetes clinic. In a group of 279 white patients attending a diabetes clinic in Cape Town, the respective rates were 34%, 9% and 24%.

Seftel already established in 1966 that both diabetes retinopathy and nephropathy were common in black diabetes patients.⁸⁵ He found evidence of retinopathy in 11% of 50 new patients (duration of diabetes less than 1 year) and in 45% of 62 'old' patients (duration of diabetes more than 3 years). Proteinuria was present in 8% and 29% respectively.

In a prospective study of 66 consecutive black patients below the age of 30 years with IDDM, Gill, *et al.*¹⁷ found cataracts in 8%, neuropathy in 16%, retinopathy in 8%, pulmonary tuberculosis in 7%, and anaemia in 3%. The majority of these complications were unidentified prior to the study.

Radiological evidence of chronic calcific pancreatitis (probably alcohol-related) was present in 45% of 25 consecutive patients with both diabetes and active pulmonary tuberculosis admitted to Pelonomi Hospital.⁸⁶ Since tuberculosis is endemic in the black and coloured population, diabetes patients may be particularly vulnerable.

At the Pelonomi Hospital diabetes clinic it was found that the detection rate for retinopathy through dilated pupils by direct ophthalmoscopy was only 65% of the rate detected by non-mydratic fundus photography.⁸⁷ Where feasible, fundus photography in adjunct to funduscopy may contribute substantially to the detection rate of diabetes retinopathy. This may be of considerable importance since diabetes eye disease is considered the leading cause of blindness in the Western world.⁸⁸

Microvascular complications were altogether common among 543 blacks, with diabetes, studied in the Zambian copperbelt.⁸⁹ Neuropathy was present in 31%, retinopathy in 34% and nephropathy in 22% to 27% of patients. Evidence of autonomic neuropathy as determined by simple clinical

tests, was present in 72% of a group of 70 randomly selected patients from the Baragwanath Hospital diabetes clinic.⁹⁰

In summary, although accurate figures are not available, it is clear from these small studies that diabetic microvascular complications are common in South Africans with diabetes, both IDDM and NIDDM of all ethnic groups, and that black NIDDM patients may be especially vulnerable to diabetes nephropathy, possibly secondary to the high rate of hypertension in this group.

Macrovascular complications

In his early series of 207 Indian diabetes patients admitted to hospital, Cosnett⁴⁰ reported hypertension in 30%, peripheral vascular disease in 9%, cerebrovascular accidents in 6% and coronary thrombosis in 1,4%. Ischaemic heart disease was considered to be present in 30% of a group of 122 Indian diabetes patients older than 40 years attending a clinic in Durban.³⁹ This rate was about the same (28%) as that found in Indians with diabetes of the same age encountered in a survey, and slightly greater than the rate found in non-diabetes patients (27%) also older than 40 years encountered in the same survey.⁴⁰ Slightly more known diabetes patients in this survey of Indian subjects were hypertensive (47%) than discovered diabetes patients (38%) while only 21% of the group of Indian clinic patients was hypertensive.

The effect of insulin therapy on blood pressure was examined in a group of 80 NIDDM patients with secondary failure.⁹¹ A significant rise in both systolic and diastolic blood pressure was noted over a three-month period after initiating insulin therapy. Patient's initial weight was predictive of the subsequent magnitude in blood pressure elevation, the greatest rise occurring in the group that were most overweight at the onset. Although at least part of the rise in blood pressure was due to weight gain, it was suggested that it may have been an insulin-mediated phenomenon.

An outstanding feature of Seftel's study of black diabetes patients was the rarity of ischaemic heart disease. ST segment depression of ≥ 1 mm on resting ECG was present in 8% and 6% of his new and old diabetes patients respectively.⁸⁵ Hypertension was present in 44% and 55% of subjects respectively and may have contributed to ST segment depression. Twelve percent of the new and 44% of the old subjects had cholesterol levels $\geq 6,5$ mmol/l. These findings were in keeping with the low prevalence of CHD in the general black population as pointed out by Walker.⁹² They calculated the annual incidence of myocardial infarction for the population of Soweto to be 10/100 000 as compared to 400/100 000 for Scotland. The actual prevalence of CHD in the black population of South Africa as well as in black diabetes patients is unknown. More than 30 years have elapsed since the prevalence of CHD in blacks with diabetes was studied. This association needs urgent attention.

In his description of diabetes mellitus in the Johannesburg African, Seftel⁹³ noted that in 250 new patients only 8 (3,2%) presented with stroke and 1 with peripheral vascular disease and gangrene. Diabetes was diagnosed in 10,4% black patients with stroke seen at Kalafong Hospital, Pretoria.⁹⁴ In this study successive patients with stroke were analysed for the presence of risk factors. The role of diabetes as a risk factor for stroke in black patients has not been studied adequately and needs to be prospectively addressed.

Haemostatic factors were examined in 33 black and 32 white diabetes subjects and compared with those in 19 normal black and 19 normal white subjects.⁹⁵ On comparing white diabetes subjects and their controls, both fibrinogen and factor VIII levels were statistically higher in the diabetes group. In blacks with diabetes, functional AT III levels were significantly raised compared to controls. These results would suggest the presence of a hypercoagulable state in the white diabetes subjects and a protective anticoagulant reaction in the blacks. When white and black diabetes subjects were compared, it was demonstrated that factor V was higher in white females, factor VII was raised in both white males and white females and that AT III was depressed in the white group as a whole. The factor VIII level was the only exception and was considerably higher in the black

group. This feature is considered to be a racial characteristic. Interestingly, this study failed to demonstrate hyperactive platelets in the majority of white and black diabetes patients.

In a study unique to Africa, McLarty, *et al.*⁹⁶ reported on the course and prognosis of 1 250 Tanzanian diabetes patients followed for 6 years. From this group 205 (16,4%) were known to have died and a further 71 patients (5,7%) were likely to have died. Mortality was highest in the six months after presentation during which time 42,4% of deaths occurred. In patients requiring insulin, diabetic keto-acidosis and infections including pulmonary tuberculosis were important causes of death. In patients not requiring insulin, cardiovascular, renal and liver diseases were important causes of mortality. These authors stressed the problems of follow up of patients with chronic diseases in Africa.

Although heart disease and specifically CHD is regarded as the leading cause of death for blacks and whites in the United States,⁹⁷ the contribution of diabetes to CHD mortality in US blacks is unknown. Similarly, in a symposium addressing diabetes in blacks in the United States the issue of CHD was also not addressed.⁹⁸

Urgent studies are needed to address the prevalence and incidence of long-term complications of diabetes in African blacks. Likewise, data on survival rates and causes of death in black patients suffering from diabetes are crucial.

ECONOMIC ASPECTS OF DIABETES MELLITUS

Diabetes is a lifelong disorder with a major influence on the provision of health care. The economic cost of diabetes should be evaluated against morbidity, premature mortality, employment, productivity and the use of health service resources.¹

Diabetes patients are admitted to hospital more often than other patients and stay longer in hospital. In England and Wales in 1981, patients with diabetes accounted for 2,8% of total hospital admissions and in the USA in 1983, diabetes patients accounted for 7,2% of total admissions.¹ To judge the impact of diabetes on inpatient facilities, hospital bed occupancy would be preferable to admission rates since many diabetes complications necessitating admission, require relative long hospital stays, e.g. foot problems, poor metabolic control and infections.

In the United States most hospitalisations for diabetes complications were for cardiovascular disease. Diabetes patients were 22 times more likely to be admitted for skin ulcers and gangrene, 15 times more for peripheral vascular disease, 10 times more for atherosclerosis, and 6-10 times more frequently for heart disease and cerebrovascular accidents.⁹⁹

The direct and indirect costs of diabetes during 1987 in the United States were estimated to be \$20.4 billion.¹⁰⁰ Direct medical costs accounted for 47,1% of total costs; indirect costs accounted for 52,9% of the total. Institutional care accounted for 38,6% of total costs, outpatient care 8,5%, premature mortality 36,8%, long-term disability 15,4%, and short-term morbidity 0,7%.

The only useful study on the costs of diabetes care in developing countries comes from Tanzania.¹⁰⁰ Direct outpatient costs amounted to \$229 per year for diabetes patients requiring insulin, and \$69 per year for those not requiring insulin. Of the \$229 for insulin-requiring diabetes patients, \$156 (68,2%) was for the provision of insulin. The total direct cost of diabetes care in Tanzania amounted to \$4 million a year and represented 8% of the total Government Health budget (compared to 4-5% of that for the United Kingdom). The average annual per capita income in Tanzania was \$160-\$200. The authors concluded that in spite of the low prevalence of diabetes in Tanzania, diabetes placed a severe strain on the limited resources of that country. Furthermore, should African patients with diabetes have to pay for their own treatment most will be unable to do so and will die. Presently no figures are available on the costs of diabetes care in South Africa. Research is urgently needed to address this issue in South Africa as well.

Diabetes has become a global problem with the frequency of IGT greatest in developing countries. Diabetes in adults is no longer a problem mainly restricted to developed and affluent societies, it is increasingly becoming a major health threat to developing societies as well.

HEALTH SERVICES

There is a paucity of published data evaluating the care of and health service provision for diabetes patients in this country. A study evaluating diabetes care in the public sector primary health care facilities in Cape Town has been completed and the results should be available in 1996. The study included record reviews, clinical examination of patients, interviews with patients as well as staff, and will provide an assessment of the quality of care in this sector. Information in the following areas will become available:

- Knowledge, attitudes and practices of diabetes clinics principle staff members in the larger day hospitals in Cape Town.
- Operations research of three large day hospital diabetes clinics determining their efficiency by recording numbers of staff, patients, and the time spent by patients with the various health workers, including nurses, doctors and pharmacists, waiting times at registration, clinic review and pharmacy.
- The patients' attendance pattern.
- The degree of glycaemic and blood pressure control achieved and prescribing practices.
- The frequency of basic clinical and biochemical examinations, for example, blood glucose, urine dipstick, weight and blood pressure measurements, as well as foot and ophthalmologic examination.
- The prevalence of chronic complications i.e. retinopathy, cataracts, nephropathy, peripheral neuropathy and peripheral vascular disease, as determined by clinical examination conducted by the researchers in comparison with that documented in the medical records.
- Patient's knowledge of the symptoms of diabetes emergencies and complications, their attitude to their disease and level of satisfaction with and attitude towards the health service.
- Factors experienced by patients which affect the pattern of their attendance and disease outcome.

This multifaceted study will provide useful information on the quality of care offered to diabetes patients at the primary care level in Cape Town, which should be generalisable to the rest of the country. Further, it will constitute baseline data prior to the institution of interventive measures to improve the health services and will facilitate its subsequent reassessment.

As part of a review, and in order to provide further information on the health services for diabetes patients in the country, a basic questionnaire was devised and sent to tertiary and secondary hospitals. Only two of the centres, which were approached did not respond, nonetheless a number of centres were omitted. The information obtained, is indicated in the Tables on pages 119 - 122 and includes:

The number of diabetes clinics and patients attending;

The staff composition, availability of specialist clinics and services;

Inpatient numbers.

TERTIARY INSTITUTION	NPA:		TPA:					CPA:			OFS:	
	King Edward VIII	Garankua	Johannesburg	HF Verwoerd	Baragwanath	Tygerberg	Groote Schuur	Red Cross Childrens	Pelonomi	National		
Times/week Diabetes Clinic operates	2	2	2 (& Poly Clinic)	3	1	5	2	3-4	1	1		
N patients/clinic	37	100		30	150	20-30		30				
N patients/week	75	200	128	90		100-135	±150		142	11		
N patients/month	300	800	500	270	600	400-500			568	44		
Medical Staff: MO		1	3+5	1		5	3		1	1		
Registrars	1	1	2	1	5	1	3	1	2	1		
Physicians	1	2	6	2	2		3	2	2	1		
Endocrinologist	4	1	6	1		2	3	1	1	Intermit		
Nursing Staff: Educators	1		5 (f/time) 3 (p/time)	1	2	2	4	1		1		
PHCS		1										
Sisters		1		1	4-6	2	4	1	1	1		
Nurses		4	1	3			6			1		
Staff Nurses						3			2	1		
Paramedical Staff: Chiroprapist			1	1	1		1			1 Intermit		
Dietitian	1	Intermittent	1	1		1	2	1	1	1		
Social Worker				1	1	1	1	1				
Pharmacist		1		1		1						

SECONDARY INSTITUTION	CPA:							
	NPA:	Edendale	Kimberley	Galeshowe Day Hospital	Cecilia Makiwane	Frere	George	Knysna
Times/week Diabetes Clinic operates	1	Seen in MOPD	Alternate weeks	MOPD/ GOPD	1	1	GOPD	
N patients/clinic		12	53					
N patients/week	155	46			20-25	5-6	20-30	
N patients/month	623	184	106		100-120		85-100	
Medical Staff: MO	3-4	1			1	1		
Registrars	3-4				1			
Physicians		1			1			
Endocrinologist								
Nursing Staff: Educators	1					1		
PHCS		1			1			
Sisters	4	1			1	2		
Nurses	1	1			1			
Staff Nurses	2				1	1		
Paramedical Staff: Chiroprapist								
Dietitian		1			1	Occasionally	1	
Social Worker		1						
Pharmacist	4				1		1	

TERTIARY INSTITUTION: SPECIALISED CLINICS	NPA: King Edward VIII	TPA:					CPA:				OFS:		
		Garankua	Johannesburg	HF Verwoerd	Baragwanath	Tygerberg	Groote Schuur	Red Cross Childrens	Pelonomi	National			
N patients/week: Renal clinic			6					no					
Pregnancy clinic			10		12-15			yes					
Paediatric clinic			10					yes					
Eye clinic								yes					
Review clinic							6						
N diabetes patients admitted/week(/month)		12 (50)	10 (40)	4 (12)	36 (145)	6-10 (30-40)	6-8 (24-32)	4 (16)					
Access to: Ophthalmologist	yes	yes	yes	yes	yes			yes	yes	yes	yes	yes	yes
Nephrologist	yes	yes	yes	yes	yes			yes	yes	yes	no	no	no

SECONDARY INSTITUTION:	CPA:						
	NPA:	Kimberley	Galeshowe Day Hospital	Cecilia Makiwane	Frere	George	Knysna
SPECIALISED CLINICS	Edendale						
N patients/week:							
Renal clinic				no	no		
Pregnancy clinic				no	no		
Paediatric clinic				no	no		
Eye clinic				no	no		
Review clinic				no	no		
N diabetes patients admitted/week(/month)	17 (98)	5 (20)				1-2 (20-25)	(7)
Access to:							
Ophthalmologist	yes	yes		yes	yes	no	yes
Nephrologist	no	no		no	yes	no	yes

CONCLUSIONS AND SUGGESTED DIRECTIONS FOR FUTURE RESEARCH

It is apparent that the major thrust of community-based diabetes research has been in the description of prevalence and risk factors for NIDDM. Early studies (1960s-1970s) included all the major communities, but recent data are available only for the black and Indian populations. Small hospital-based studies have been conducted to determine the frequency of microvascular complications and acute metabolic emergencies. Future community-based diabetes research as detailed below, should encompass health systems research, epidemiological studies, determination of health care costs and interventional studies. A workshop for those interested in these areas could be held to prioritize the studies and to standardise research methodologies.

I HEALTH SERVICES

This is a priority area and studies should be planned to facilitate the ongoing development, maintenance and evaluation of public health services capable of providing good quality care for patients with this chronic disorder nationally. Suggested studies include:

- **Basic documentation of the health services** available for diabetes patients throughout the country at primary, secondary and tertiary level should be undertaken to establish the current situation. This should include numbers of clinics, staff complement and level of training, equipment, patient numbers, staff-patient ratios, drug availability and methods to determine glycaemic control and the presence of complications.
- **Assessment of knowledge levels and practices of diabetes clinic staff** at primary and secondary settings either nationally, or alternatively and more realistically in certain selected areas will also be required.
- **An evaluation of the quality of care** provided by these services should be undertaken by the health services, using specific measures of practice and outcome in collaboration with researchers in the area.
- The efficiency and efficacy of the services provided should be determined.

II ECONOMIC ASPECTS OF DIABETES

The **direct and indirect costs of diabetes** should be determined to establish the extent of the burden this disease currently places on the health budget, which should provide further impetus to the institution of primary and secondary interventional programmes.

Standards of care and treatment protocols for diabetes should be formulated by local experts drawn from academic institutions, SEMDSA, clinicians and representatives from the health services.

An audit of the quality of care provided by health services should be repeated following the institution of the guidelines for diabetes care.

Investigation of the level of diabetes awareness among health care workers in the context of cardiovascular risk factors would provide valuable information for those attempting to promote early detection of these risk factors.

III EPIDEMIOLOGY - *NIDDM*

The **prevalence and risk factors for NIDDM and IGT in the coloured and white population** would complete the picture of the epidemiology of NIDDM in this country and enable appropriate planning

of national primary interventive studies.

Longitudinal studies should be designed to determine changes in prevalence rates in NIDDM and its associated diseases, e.g. hypertension, following the institution of primary interventive measures to determine their efficacy. These interventions should be directed towards a decrease in the rate of obesity, increase in physical activity and stimulating healthy eating habits.

Studies of the incidence and prevalence of complications of NIDDM in different ethnic groups should be studied. This could be conducted by interested workers at academic institutions, secondary hospitals, and primary level clinics using a revision of the WHO complication study protocol.

Mortality rates of NIDDM should be determined by interested researchers drawn from the Medical Research Council, Community Medicine and Social Science Departments and academic diabetes Units.

Studies of the genetics of NIDDM would contribute to an understanding of the pathogenesis of the disease. These should be undertaken by academic institutions and may involve collaboration with interested groups in the USA and Europe.

- IDDM

The incidence of IDDM should be determined by the institution of a national register of patients through involvement of academic diabetes units, secondary hospital staff, general practitioners, and public sector primary level staff.

Evaluation of the incidence and prevalence of complications (both acute metabolic and chronic microvascular) in IDDM as well as an audit of the quality of care of IDDM should be undertaken by academic diabetes units where most IDDM are managed. The institution of a national register for IDDM would facilitate these studies.

Studies of genetic and immunology of IDDM are currently in progress and involve the major academic diabetes units in the country.

REFERENCES

1. Pickup JC, Williams G. *Textbook of Diabetes*. Oxford: Blackwell Scientific Publications, 1991:37.
2. WHO Expert Committee. *Diabetes Mellitus*. (Technical Report Series No. 727). Geneva: World Health Organisation, 1985.
3. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979;28:1039-1057.
4. Jarrett RJ. Do we need IGT? *Diabet Med* 1987;4:544-545.
5. Yudkin JS, Alberti KGMM, McLarty DG, *et al.* Impaired glucose tolerance: Is it a risk factor for diabetes or a diagnostic ragbag? *BMJ* 1990;301:397-401.
6. Keen, Jarrett RJ, McCartney P. The ten-year follow-up of the Bedford Survey (1962-1972): Glucose tolerance and diabetes. *Diabetologia* 1982;22:73-78.
7. Fuller JF, Shipley MJ, Rose G, *et al.* Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall Study. *Lancet* 1980;i:1373-1375.
8. Seftel HC, Keeley KJ, Walker ARP. Studies in glycosuria and diabetes in non-white populations of the Transvaal. *SAMJ* 1963;37:1213-1216.
9. Walker ARP. Nutritional, biochemical and other studies on South African populations. *SAMJ* 1966;44:814-852.

10. Rwiza HT, Swai BM, McLarty DG. Failure to diagnose diabetic ketoacidosis in Tanzania. *Diabet Med* 1986;3:181-183.
11. Jackson WPU. Epidemiology of diabetes in South Africa. *Adv Metab Disord* 1978;9:111-146.
12. Omar MAK, Motala AA, Seedat MA, *et al.* South African Indians show a high prevalence of NIDDM and bimodality in plasma glucose distribution patterns. *Diabetes Care* 1994;17:70-73.
13. Asmal AC, Jialal I, Leary WP *et al.* Insulin-dependent diabetes mellitus with early onset in blacks and Indians. *SAMJ* 1981;60:91-93.
14. Gill GV, Huddle KR. Patterns of insulin dependence in an African diabetic clinic. *Q J Med* 1991;81:829-835.
15. Edeling J, Mollentze WF, Steyn AF. *Clinical characteristics of black subjects at their first visit to a diabetic clinic.* Congress Proceedings. Durban: Society for Endocrinology, Metabolism and Diabetes of Southern Africa, March 1992.
16. Omar MAK, Asmal AC. Patterns of diabetes mellitus in young Africans and Indians in Natal. *Trop Geogr Med* 1984;36:133-138.
17. Gill GV, Huddle KR. Patterns and problems of diabetes in Soweto. *Central Afr J Med* 1984;30:189-195.
18. Kalk WJ, Huddle KRL, Raal FJ. The age of onset and the sex distribution of insulin-dependent diabetes mellitus in Africans in South Africa. *Postgrad Med J* 1993;69:552-556.
19. Omar MAK, Asmal AC. C-peptide response to glucagon in black and Indian insulin-dependent diabetics. *SAMJ* 1981;61:395-397.
20. Omar MAK, Botazzo GF, Asmal AC. Islet cell antibodies and other autoantibodies in South African blacks and Indians with insulin-dependent diabetes mellitus (IDDM). *Horm Metabol Res* 1986;18:126-128.
21. Kalk WJ, Kruger M, Slabbert A, *et al.* Fat, protein and carbohydrate content of diets of white insulin-dependent diabetic adolescents and young adults. *SAMJ* 1992;81:399-402.
22. Segal I, Joffe BI, Walker ARP, *et al.* Glycaemic responses to different carbohydrate foods in healthy and diabetic blacks in Soweto. *SAMJ* 1991;80:546-549.
23. Elamin A, Omer MIA, Hofvander Y, *et al.* Prevalence of IDDM in schoolchildren in Khartoum, Sudan. *Diabetes Care* 1989;12:430-432.
24. McLarty DG, Pollitt C, Swai ABM. Diabetes in Africa. *Diabet Med* 1990;7:670-684.
25. Seftel HC, Abrams GJ. Diabetes in the Bantu. *BMJ* 1960;April 16:1207-1208.
26. Politzer WM, Schneider T. Diet and diabetes mellitus: Possible relationships. A comparative study in a rural and urban community. *SAMJ* 1962;36:608-610.
27. Goldberg MD, Marine N, Ribeiro F, *et al.* Prevalence of glycosuria and diabetes among Indians and Bantu. *SAMJ* 1969;43:733-738.
28. Marine N, Vinik AI, Edelstein I, *et al.* Diabetes, hyperglycaemia and glycosuria among Indians, Malays and Africans (Bantu) in Cape Town, South Africa. *Diabetes* 1969;18:840-857.
29. Walker ARP. *Urbanisation of developing populations: Bearing of rise in privilege and the prevalence of diseases of nutritional deficiency and excess.* In: Chaves A, Bourges H, Basta S eds. Proceedings 9th International Congress Nutrition, Mexico 1972. Basel: Karger, 1975:26-31.
30. Seedat YK, Mayet FGH, Latiff GH, *et al.* Risk factors and coronary heart disease in Durban blacks - the missing links. *SAMJ* 1992;82:251-256.
31. Omar MAK, Seedat MA, Motala AA, Dyer RB, Becker P. The prevalence of diabetes mellitus and impaired glucose tolerance in a group of urban South African blacks. *SAMJ* 1993;83:641-643.
32. Levitt NS, Katzenellenbogen JM, Bradshaw D, *et al.* The prevalence and risk factors for NIDDM in Urban Africans in Cape Town, South Africa. *Diabetes Care* 1993;16:601-607.
33. Mollentze WF, Moore A, Oosthuizen GM, *et al.* The prevalence of diabetes mellitus in two South African black populations. Abstract. *Diabetologia* 1992;35 (Suppl 1):511.
34. McLarty DG, Swai ABM, Kitange HM. Prevalence of diabetes and impaired glucose tolerance in rural Tanzania. *Lancet* 1989;i:871-875.
35. Ahrén B, Corrigan CB. Prevalence of diabetes mellitus in North-western Tanzania. *Diabetologia* 1984;26:333-336.
36. Fisch A, Pichard E, Prazvck T, *et al.* Prevalence and risk factors of diabetes mellitus in the rural region of Mali (West Africa): A practical approach. *Diabetologia* 1987;30:859-862.
37. Harris MI, Hadden WC, Knowler WC, *et al.* Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20-74 yr. *Diabetes* 1987;36:523-534.
38. Dowse GK, Zimmet PZ, King H. Relationship between prevalence of impaired glucose tolerance and NIDDM in a population. *Diabetes Care* 1991;14:968-974.
39. Cosnett JE. Illness among Natal Indians: A survey of hospital admissions. *SAMJ* 1957;31:1109-1115.
40. Cosnett JE. Diabetes among Natal Indians. *BMJ* 1959;Jan 24:187-192.
41. Wood MM. A glycosuria survey in an Indian community. *Med Proc* 1960;26:140-141.
42. Campbell GD. Diabetes in Asians and Africans in and around Durban. *SAMJ* 1963;37:1195-1208.
43. Campbell GD. Insulin-independent young diabetics in Natal. *BMJ* 1960;Aug 13:537-538.
44. Jialal I, Joubert SM, Asmal AC, *et al.* The insulin and glucose response to an oral glucose load in non-insulin-dependent diabetes in the young. *SAMJ* 1982;61:351-354.
45. Jialal I, Joubert SM. Obesity does not modulate insulin secretion in Indian patients with non-insulin-dependent diabetes in the young. *Diabetes Care* 1984;7:77-79.
46. Omar MAK, Seedat MA, Dyer RB, *et al.* The prevalence of diabetes mellitus in a large group of South African Indians. *SAMJ* 1985;67:924-926.
47. Motala AA, Omar MAK, Gouws E. High risk of progression to NIDDM in South African Indians with impaired glucose tolerance. *Diabetes* 1993;42:556-563.
48. Jackson WPU, Vinik AI, Joffe BI, *et al.* Prevalence of diabetes, glycosuria and related variables among the white population in Cape Town. *SAMJ* 1969;43:1496-1499.
49. Michael C, Edelstein I, Whisson A, *et al.* Prevalence of diabetes, glycosuria and related variables among a Cape coloured population. *SAMJ* 1971;45:795-801.
50. Ranchod HA, Vaughan JE, Parvis P. Incidence of gestational diabetes at Northdale Hospital, Pietermaritzburg. *SAMJ* 1991;80:14-16.
51. Jackson WPU, Coetzee EJ. Glycosuria as an indication for glucose tolerance testing during pregnancy. *SAMJ* 1979;56:921-923.
52. Huddle K, England M, Najjar A. Outcome of pregnancy in diabetic women in Soweto, South Africa 1983-1992. *Diabet Med* 1993;10:290-294.
53. Omar MAK, Asmal AC. Family histories of diabetes mellitus in young African and Indian diabetics. *BMJ* 1983;286:1786.
54. Omar MAK, Hammond MG, Seedat MA, *et al.* HLA antigens and non-insulin-dependent diabetes mellitus in young South African Indians. *SAMJ* 1985;67:130-132.
55. Briggs BR, Jackson WPU, Du Toit ED, *et al.* The histocompatibility (HLA) antigen distribution in Southern African blacks (Xhosa). *Diabetes* 1980;29:68-70.
56. Shires R, Maier G, Lustig A, *et al.* HLA antigens in white and black South African diabetics. *SAMJ* 1983;64:1087-1089.
57. Asmal AC, Dayal B, Jialal I, *et al.* Non-insulin-dependent diabetes mellitus with early onset in blacks and Indians. *SAMJ* 1981;60:93-96.

58. DeFronzo RA. Pathogenesis of Type 2 (non-insulin-dependent) diabetes mellitus: A balanced overview. *Diabetologia* 1992;35:389-397.
59. Rubenstein AH, Seftel HC, Miller K, *et al.* Metabolic response to oral glucose in healthy South African white, Indian, and African subjects. *BMJ* 1969;March 22:748-751.
60. Jackson WPU, van Mieghem W, Keller P. Insulin excess as the initial lesion in diabetes. *Lancet* 1972;I:1040-1044.
61. Jackson WPU, Keller P. Glucose/insulin relationships in a population sample: The 'initial lesion' of diabetes mellitus. *Hormones* 1972;3:361-374.
62. Keller P, Schatz L, Jackson WPU. Immunoreactive insulin in various South African population groups. *SAMJ* 1972;46:152-157.
63. Wicks ACB, Jones JJ. Insulinopenic diabetes in Africa. *BMJ* 1973;1:773-776.
64. Joffe BI, Goldberg RB, Seftel HC, *et al.* Insulin, glucose and triglyceride relationships in obese African subjects. *Am J Clin Nutr* 1975;28:616-620.
65. Asmal AAC, Leary WP. Carbohydrate tolerance, plasma insulin, growth hormone and lipid levels in Indian and black diabetics. *SAMJ* 1975;49:810-812.
66. Shires R, Joffe BI, Seftel HC. Hormonal and metabolic responses to an oral glucose load in obese black diabetics. *SAMJ* 1978;53:446-448.
67. Shires R, Joffe BI, Seftel HC. Maximal pancreatic beta-cell stimulation and the counter-regulatory hormonal responses in South African black and white obese subjects. *SAMJ* 1985;67:845-847.
68. Panz VR, Raal FJ, Joffe BI, *et al.* Insulin-receptor activity in nondiabetic and diabetic urbanised South African black women. *Diabetes Care* 1992;15:277-281.
69. Wing JR, Panz VR, Joffe BI, *et al.* Changes in glucose disposal and cellular insulin binding in obese black Southern African patients with Type 2 diabetes mellitus before and after sulphonylurea therapy. *Diabet Med* 1992;10:50-55.
70. Joffe BI, Panz VR, Wing JR, *et al.* Pathogenesis of non-insulin-dependent diabetes mellitus in the black populations of southern Africa. *Lancet* 1992;340:460-462.
71. Hales CN, Barker DJP. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992;35:595-601.
72. Joffe BI, Seftel HC. Diabetes mellitus in the black communities of Southern Africa. *J Int Med* 1994;235:137-142.
73. Ekoe JM. Epidemiology of non-insulin-dependent diabetes mellitus (NIDDM). *Diab Res Clin Prac* 1988;4(suppl 1):66-70.
74. Home PD. Diagnosing the undiagnosed with diabetes. *BMJ* 1994;2:436.
75. Panzram G. Mortality and survival in Type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1987;30:123-131.
76. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595-1607.
77. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridaemia, and hypertension. *Arch Intern Med* 1989;149:1514-1520.
78. Central Statistical Services. *Deaths of Blacks: 1990.* (Report No. 03-10-01). Pretoria: Government Printer, 1990.
79. Buch E, Irwig LM, Huddle KR, *et al.* Pointers to preventing hyperglycaemic emergencies in Soweto. *SAMJ* 1983;64:705-709.
80. Huddle HR, Gill GV. Reducing acute hyperglycaemic mortality in African diabetic patients. *Diabet Med* 1989;6:64-66.
81. Gill GV, Huddle KR. Hypoglycaemic admissions among diabetic patients in Soweto, South Africa. *Diabet Med* 1993;10:181-183.
82. Rostand SG. Diabetic renal disease in blacks - inevitable or preventable? *N Engl J Med* 1989;321:1121-1122.
83. Seedat YK, Naicker S, Rawat R, *et al.* Racial differences in the causes of end-stage renal failure in Natal. *SAMJ* 1984;65:956-958.
84. Jackson WPU, Goldberg MD, Major V, *et al.* Vascular and other diabetes-related disorders among Natal Indian diabetics and non-diabetics. *SAMJ* 1970;44:279-285.
85. Seftel HC, Walker ARP. Vascular disease in South African Bantu diabetics. *Diabetologia* 1966;2:286-290.
86. Mollentze WF, Pansegrouw DF, Steyn AF. Diabetes mellitus, pulmonary tuberculosis and chronic calcific pancreatitis revisited. *SAMJ* 1990;78:235-236.
87. Mollentze WF, Stulting AA, Steyn AF. Ophthalmoscopy versus non-mydratic fundus photography in the detection of diabetic retinopathy in black patients. *SAMJ* 1990;78:248-250.
88. Little HL, Jack RL, Patz A, *et al.* eds. *Diabetic retinopathy.* New York: Thieme-Stratton, 1983:17.
89. Rolfe M, Armstrong JRM. Diabetes mellitus on the Zambian copperbelt. *J Royal Col Phys* 1989;23:255-259.
90. Morley JE, Asvat MS, Klein C, *et al.* Autonomic neuropathy in black diabetic patients. *SAMJ* 1977;52:115-116.
91. Randeree HA, Omar MAK, Motala AA, *et al.* Effect of insulin therapy on blood pressure in NIDDM patients with secondary failure. *Diabetes Care* 1992;10:1258-1263.
92. Walker ARP, Walker BF. Coronary disease in blacks in underdeveloped populations. *Am Heart J* 1985;109:1410.
93. Seftel HC, Schultz E. Diabetes mellitus in the urbanised Johannesburg African. *SAMJ* 1961;35:66-70.
94. Rosman KD. The epidemiology of stroke in an urban black population. *Stroke* 1986;17:667-669.
95. Adelstein S, Gomperts ED, Joffe BI, *et al.* Haemostatic factors in black and white diabetics. *SAMJ* 1979;55:325-328.
96. McLarty DG, Kinabo L, Swai ABM. Course and prognosis. *BMJ* 1990;300:1107-1110.
97. Saunders E ed. *Cardiovascular Diseases in Blacks.* Philadelphia: FA Davis Company, 1991:3.
98. Gavin JR, Goodwin N. Diabetes in black populations: Current state of knowledge. *Diabetes Care* 1990;13(Suppl 4):1139-1208.
99. Bransome ED. Financing the cost of diabetes mellitus in the 1990s. *Diabetes Care* 1992;15(Suppl 1):1-72.
100. Chale SS, Swai AB, Mujinja PG, *et al.* Must diabetes be a fatal disease in Africa? Study of costs of treatment. *BMJ* 1992;304:1215-1218.