

# DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE IN SOUTH AFRICA

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

Diabetes mellitus is a diverse group of metabolic disorders with varied clinical characteristics united by hyperglycaemia, the final common biochemical abnormality. The ever-expanding knowledge base of diabetes necessitates the periodic review of its classification and diagnostic criteria. Thus, in 1998 the World Health Organization (WHO) published a revised classification and diagnostic criteria for diabetes that followed the American Diabetes Association's (ADA) extensive review of the subject.<sup>1</sup> These diagnostic criteria for diabetes and other categories of hyperglycaemia<sup>1</sup> are shown in Table 10.1.

Table 10.1. Values for the diagnosis of diabetes mellitus and other categories of hyperglycaemia

	Venous plasma glucose (mmol/L)
<b>Diabetes mellitus:</b>	
Fasting	≥ 7.0
or	
2-h post glucose load	≥ 11.1
or both	
<b>Impaired glucose tolerance (IGT):</b>	
Fasting concentration (if measured)	< 7.0
and	
2-h post glucose load	≥ 7.8 and < 11.1
<b>Impaired fasting glycaemia (IFG):</b>	
Fasting*	≥ 6.1 and < 7.0
2-h (if measured)	< 7.8

\* The ADA recently proposed that the upper limit of normal for fasting plasma glucose be lowered to 5.6 mmol/L<sup>2</sup>

Adapted from Alberti *et al.*<sup>3</sup> (1998)

The WHO state for epidemiological or population-screening purposes, the fasting and/or 2-hour value after 75 g oral glucose may be used. If the oral glucose tolerance test (OGTT) cannot be performed, the WHO recommends that fasting plasma glucose alone can be used for epidemiologic purposes.<sup>1</sup>

Since the publication of the ADA and the revised WHO criteria, it became evident that the exclusive use of fasting plasma glucose to diagnose diabetes has an effect on the prevalence of diabetes, the phenotype identified, the ability of IFG to predict diabetes as well as cardiovascular disease and mortality.<sup>4</sup>

The WHO<sup>1</sup> also proposed a new classification system encompassing both clinical stages and aetiological types of diabetes mellitus and other categories of hyperglycaemia. The clinical stages include normal glucose tolerance, IGT or IFG, not insulin requiring and, finally, insulin requiring. These stages, regardless of their aetiology, progress through several clinical stages during their natural history. The stage of glycaemia may change over time depending on the extent of the underlying disease processes. Individual subjects may move from stage to stage in either direction.<sup>1,3</sup>

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The classification by aetiological type results from improved understanding of the causes of diabetes. The aetiological classification reflects the fact that the defect or process, which may lead to diabetes, may be identifiable at any stage in the development of diabetes - even at the stage of normoglycaemia. The severity of the metabolic abnormality can either regress (e.g. with weight reduction), progress (e.g. with weight gain), or stay the same. According to residual beta-cell function some individuals may need insulin for survival, while others according to the severity of the underlying metabolic abnormality, may need insulin for adequate glycaemic control.<sup>1</sup>

The WHO working group eliminated the terms 'insulin-dependent diabetes mellitus' and 'non-insulin-dependent diabetes mellitus' and their acronyms 'IDDM' and 'NIDDM'.<sup>1</sup> These terms were confusing and frequently resulted in patients being classified based on treatment rather than on pathogenesis. The terms type 1 and type 2 were retained.<sup>3</sup> The aetiological type named type 1 is primarily caused by pancreatic islet beta-cell destruction and is prone to ketoacidosis. Type 1 diabetes includes those cases attributable to an autoimmune process, as well as those with beta-cell destruction and who are prone to ketoacidosis for which aetiology and pathogenesis is unknown (idiopathic). It does not include those forms of beta-cell destruction or failure to which specific causes can be assigned (e.g. cystic fibrosis, mitochondrial defects).

## THE PREVALENCE OF GLUCOSE INTOLERANCE AND ASSOCIATED RISK FACTORS IN SOUTH AFRICAN POPULATIONS

Few epidemiological studies have been conducted and reported since 1994. South Africa's first demographic and health survey, a landmark study, was conducted during 1998. In this, 13 827 adults (15 years and over) were interviewed.<sup>3</sup> There was a response rate of 93% with more than 60% of respondents living in urban areas. The self-reported prevalence of diabetes in males and females  $\geq 15$  years was 2.4% and 3.7%, respectively (see table). As expected, the Asian Indian community had the highest self-reported prevalence, followed by the coloured, white and black African groups. The prevalence of diabetes in urban males was 2.9% and urban females 4.4%, compared to 1.7% and 2.7% in the non-urban men and women, respectively. There was considerable geographic variation in the prevalence of diabetes. The highest prevalences were found in KwaZulu-Natal, Western Cape and Gauteng and the lowest in the Limpopo and North West Provinces.

Table 10.2. DHS: Self-reported prevalence of diabetes (%) in men and women  $\geq 15$  years by province and population group

Province	Women	Men
Western Cape	4.9	3.2
Eastern Cape	3.5	2.7
Northern Cape	2.9	2.1
Free State	2.3	1.3
KwaZulu-Natal	5.9	3.1
North West	1.1	0.9
Gauteng	4.3	3.3
Mpumalanga	2.8	2.0
Limpopo	1.2	0.9
Population group		
Black African	3.0	1.6
Urban	3.7	1.6
Rural	2.2	1.5
Coloured	5.8	3.1
White	4.8	6.0
Asian	11.5	8.5
Total	3.7	2.4

## CROSS-SECTIONAL PREVALENCE STUDIES

### Black African

Erasmus and co-workers examined the prevalence of diabetes in 374 factory workers in Umtata.<sup>6</sup> Using the standard 75 g OGTT, they reported an age-adjusted prevalence of diabetes and IGT of 4.5% and 5.1%, respectively. Of the nine diabetic workers, only one had been diagnosed with diabetes previously. This was a somewhat unusual finding as was the fact that obesity was not a risk factor for diabetes in this study.

A surprisingly high prevalence of diabetes has recently been reported from the rural region of the Limpopo province. This study has considerable flaws as freely acknowledged by the authors, namely a response rate of only 40% and a diagnosis of diabetes adjudged solely on fasting plasma glucose levels. Yet the diabetes prevalence was 8.8% in women and 8.5% in men.<sup>7</sup>

### Cape Town Coloured

Levitt and co-workers<sup>8</sup> studied the prevalence of diabetes in 974 residents from the mixed ancestry (coloured) community of Mamre in the Western Cape. The age-standardised prevalence of type 2 diabetes in the age group 30-65 years was 10.8% and that of IGT 10.2%. In men an inverse relationship was noted between levels of physical activity and prevalence of diabetes. Age, family history of diabetes, waist circumference and physical activity were all identified as independent risk factors for diabetes, while sex, regular alcohol consumption and BMI were not. In this study, the population attributable risk fraction for upper segment fat distribution (waist circumference) and physical inactivity were 53% and 21%, respectively. The authors estimated that the crude prevalence of diabetes in this community might be reduced from 7.1% to 4% by reversing both upper segment fat distribution and physical inactivity.

A single study specifically examined the prevalence of diabetes in the elderly. In this the prevalence of diabetes in a representative sample of 180 coloured subjects ( $\geq 65$  years) resident in Cape Town was 28% and 29% for men and women, respectively.<sup>9</sup> Previously 25% of the diabetes subjects were undiagnosed. Body mass and waist-to-hip ratio were the only risk factors identified for diabetes, leading the authors to implicate changes in body composition with age as a possible explanation for the lack of association between BMI and diabetes in this group. The high prevalence of diabetes identified in this study highlighted the need for routine screening for diabetes in elderly coloured subjects during visits to primary health-care facilities.

Differences in methodology between historic and more recent studies make it unclear whether the prevalence of diabetes is on the increase in South Africa, especially in the rapidly urbanising black communities. Longitudinal studies utilising WHO criteria are needed to resolve this issue, as well as to confirm previously identified risk factors for the development of IGT and diabetes in our diverse population groups.

Table 10.3. Recent cross-sectional diabetes prevalence studies

Setting	Population	Respondents (No)	Response Rate (%)	Age Range (yr)	BMI mean (SD)		Criteria for DM diagnosis	Age standardised prevalence (%)	
					Men	Women		Men	Women
Cape Town	Coloured	191	95.5	>65	24.0† (5.2)	28.7† (6.2)	WHO (1985)	25.7*	30.3*
Umtata	Black African	374	73	>20	23.9 (0.28)	30.4 (0.52)	WHO (1985)	4.5	4.5
Limpopo Province	Black African	1391	34	>30	23.7 (4.7)	27.2 (6.2)	ADA	8.5	8.8

† non diabetic

\* not age-standardised

Sub-Saharan African collaboration re-analysed various cross-sectional population-based epidemiological studies conducted from 1985 to 1992 in order to examine the impact of the 1997 ADA criteria on the prevalence of diabetes and IGT in African subjects.<sup>10</sup> Data were available from rural and urban communities in Cameroon (n=1 804), Tanzania (n=10 013) and South Africa (n=3 799) (Table 10.4). The prevalence of diabetes based on the ADA criteria (using only fasting glucose concentrations) was higher in all Tanzanian surveys and in four of the five South African surveys, was unchanged in one South African study, and lower in both surveys from Cameroon, than when utilising the earlier WHO criteria. The absolute change in prevalence using the new criteria was small (<2.5%) with the exception of one survey (Mara). When combining both sets of criteria, as in the new WHO criteria (i.e. both lower fasting and original post-glucose levels), the prevalence of diabetes (crude, not age-standardised) was higher in

10 of the 11 surveys. In the other survey the combined prevalence was the same as that obtained when using the WHO criteria but higher than the prevalence when utilising the ADA criteria. The prevalence of IFG was lower than the prevalence of IGT with the exception of the Mamre community in South Africa. There was a poor level of concordance in the classification of individuals as diabetic using the ADA and WHO criteria and the range in Kappa statistic between the surveys was considerable. The Kappa statistic was lowest (<0.25) in the Tanzanian surveys, intermediate in four of the South African surveys and highest (0.86 and 0.61) in the Cameroon and one of the South African surveys. This application of the new WHO criteria would increase estimates of the total prevalence of diabetes in sub-Saharan Africa. The poor level of agreement between the categories IFG and IGT in these data sets and those of others,<sup>5</sup> demonstrate that IFG and IGT are not analogous. Much of the current knowledge of the epidemiology and natural history of glucose intolerance, diabetes, and the health risks associated with them are based on the 2-h blood glucose.<sup>11</sup> Consequently, it is advisable that diabetes prevalence studies in sub-Saharan Africa should use the OGTT.

Table 10.4. The prevalence\* of diabetes and impaired glucose tolerance (IGT) classified by old WHO criteria, diabetes and impaired fasting glucose (IFG) classified by new ADA criteria and diabetes classified by new WHO criteria<sup>10</sup>

	WHO			ADA			New WHO diabetes (crude)
	Diabetes (crude)	Diabetes (age-standardised)	IGT (age-standardised)	Diabetes (crude)	Diabetes (age-standardised)	IFG (age-standardised)	
<b>Cameroon</b>							
Evoudoula	0.9	0.7	3.6	0.8	0.7	0.3	0.9
Yaounde	1.4	1.5	3.4	1.4	1.2	0.3	1.5
<b>South Africa</b>							
Cape Town	6.3	8.0	7.1	7.3	9.2	2.3	8.7
Mamre	7.1	8.5	8.1	8.4	9.8	12.1	9.4
Manguang†	7.7	8.2	14.8	9.9	10.6	9.1	11.1
QwaQwa†	6.1	6.0	12.9	5.8	6.0	3.6	7.7
Durban	3.7	4.4	9.0	4.9	5.9	4.3	5.2
<b>Tanzania</b>							
Kilimanjaro	1.0	0.8	6.9	1.7	1.2	2.0	1.8
Mara	0.8	1.3	8.4	3.5	4.1	3.9	3.8
Morogo	0.8	1.0	8.1	1.1	1.2	1.7	1.7
Dar-es-Salaam	1.1	1.4	10.6	2.0	2.5	2.7	2.3

\* Including both known and previously undiagnosed diabetes

† Age-standardised prevalence for  $\geq 30$  years

The global burden of diabetes was 124 million in 1997 and it was estimated that it will double to 221 million in 2010.<sup>12</sup> In Africa, the estimated number of diabetics in 1997 was 7.8 million, of whom 4.5 million were in North Africa, 1.08 million in Western Africa, 1.05 million in Eastern Africa, 0.26 million in Central Africa, and 0.82 million in Southern Africa.<sup>9</sup>

The impact of the HIV/AIDS epidemic on the projected prevalence of diabetes for Africa in 2010 must also be taken into account. In 1999, Panz and Joffe<sup>13</sup> assessed the impact that HIV/AIDS would have on the prevalence of type 2 diabetes in South Africa in 2010. The analysis was based upon an assumption that the population growth would fall from 1.9% in 1995 to 0.3% in 2010 because of the HIV/AIDS epidemic. They estimated that without HIV/AIDS the number of people with diabetes would increase from 1.6 million in 1995 to 3.5 million in 2010, and with HIV/AIDS to 3.4 million – a 3% reduction representing 100 000 fewer cases.<sup>10</sup> This was based on an assumed doubling of diabetes prevalence from 4% to 8%.

In 2005, Levitt and Bradshaw<sup>14</sup> re-examined this issue and extended the analysis to include the number of diagnosed cases in South Africa in 2010, since the latter is those seeking health care for diabetes. This was prompted by the availability of recent national 2001 census data, improved estimates of the burden of HIV/AIDS and estimates of the prevalence of diabetes that allow for subpopulation differences. Based on the ASSA2000 AIDS and demographic model the population growth rate in South

Africa is estimated to be 1.1% per annum in the presence of the HIV/AIDS epidemic compared with 1.8% in the absence of the epidemic.<sup>15</sup> Three different scenarios of diabetes prevalence were used: no rise, a 50% rise and a doubling. The projections calculated were based on assumptions of no changes in sexual behaviour or widespread use of anti-retroviral therapy (ART) including, for prevention of mother-to-child transmission. The number of known cases of diabetes was calculated based on evidence that approximately 50% of people with diabetes identified in local cross-sectional population studies were previously diagnosed.

As evident from Table 10.5 below, the total number of people with diabetes is going to increase, with or without the expected impact of HIV/AIDS and the extent of rise in diabetes prevalence. These data highlight the fact that South Africa, in common with other sub-Saharan African countries, should not lose sight of the impact and importance of diabetes, in the face of the HIV/AIDS epidemic. There will be a greater number of people with diabetes within the health system because of a number of factors including the ageing of the population, the expected changing prevalence of diabetes and although not included in the estimates, diabetes induced by ART.

Table 10.5. Demographic impact of HIV/AIDS on projected\* prevalence of type 2 diabetes and patient load in South Africa

	1995	2010		Decrease resulting from HIV/AIDS
		Without HIV/AIDS	With HIV/AIDS	
Population ('000s)	40 410	52 706	47 392	
Growth rate (%)		1.8%	1.1%	
<b>No increase in age-specific prevalence</b>				
Adult Prevalence (%)	3.6%	4.1%	4.1%	
Projected number of cases ('000s)	959	1 528	1 344	184
Projected patient load ('000s)	479	764	677	87
<b>50% increase in prevalence</b>				
Adult Prevalence (%)	3.6%	6.2%	6.2%	
Projected number of cases ('000s)	959	2 292	2 015	277
Projected patient load ('000s)	479	1 146	1 008	138
<b>100% increase in prevalence</b>				
Adult Prevalence (%)	3.6%	8.2%	8.1%	
Projected number of cases ('000s)	959	3 027	2 631	396
Projected patient load ('000s)	479	1 514	1 316	198

\* Projections were calculated using age-specific rates

## FOLLOW-UP STUDIES

Motala and co-workers<sup>16</sup> conducted a 10-year follow-up study on 517 Indian subjects with normal glucose tolerance or IGT at baseline with 9.5% progressing to diabetes at 10 years with an age- and sex-adjusted diabetes incidence of 8.3% (rate of progression 0.95% per annum). Significant predictive variables for subsequent diabetes development included 2-h plasma glucose, BMI, and obesity. Obese subjects had a 4.6-fold greater risk of progressing to diabetes, indicating the importance of lifestyle interventions aimed at reducing weight in diabetes prevention in this group.

Motala *et al.*<sup>17</sup> investigated the importance of transient IGT in the migrant Indian population of Durban. A 75 g OGTT was repeated after one year on 128 Indian subjects previously diagnosed with IGT. Of these, 41 progressed to type 2 diabetes, 47 remained in the IGT category, and 40 reverted to normal glucose tolerance. The non-diabetic groups were re-evaluated by OGTT three years later. Thirty-two of the 40 subjects who had reverted to normal glucose tolerance status after one year completed the study. None developed diabetes, while 11 (34%) reverted to IGT again and 21 (66%) had persistent normal glucose tolerance. The authors concluded that transient IGT (IGT at baseline and normal glucose tolerance after one year) was not associated with a risk of progression to diabetes in a group of South African migrant Indians from the U.S.A with a high prevalence of diabetes.<sup>17</sup> This finding was in contrast to what was previously reported for Pima Indians. In South African Indians, an absence of obesity and lower 2-h plasma glucose at baseline was predictive (protective) for reversion to normal glucose tolerance in the local study. On the other hand, worsening of glucose tolerance in these subjects was associated with deterioration of beta-cell secretory function.

## EPIDEMIOLOGY OF TYPE 1 DIABETES

There have been no reports on the incidence of type 1 diabetes from South Africa.

## PATHOGENESIS OF TYPE 1 DIABETES

Until recently, little was known about the role of autoimmunity in the pathogenesis of diabetes in black South Africans. In an attempt to resolve this issue, the presence of glutamic acid decarboxylase (GAD) 65 antibodies was studied in 100 black patients with type 1 diabetes (age of onset < 35 years and BMI < 27 kg/m<sup>2</sup>) and 80 black patients with type 2 diabetes (age > 35 years and BMI > 27 kg/m<sup>2</sup>).<sup>18</sup> The control group consisted of 50 healthy black subjects. Forty-four patients (44%) with type 1 diabetes were GAD antibody positive compared to two patients (2.5%) with type 2 diabetes. No patient with chronic pancreatitis or lipoatrophic diabetes was GAD antibody positive. One-third of black patients fulfilling the criteria for diabetic keto-acidosis and admitted to hospital was GAD antibody positive compared to 67% of white patients.<sup>19</sup> The black patients (mostly female) also had a greater BMI than white patients (23.1 vs. 20 kg/m<sup>2</sup>) while 28% of black patients had C-peptide levels > 0.3 nmol/L compared to none of the white patients, indicating "fair" beta-cell function in the black patients. Autoimmune beta-cell destruction thus appears to have an important role in the pathogenesis of type 1 diabetes in African subjects.

Few studies in African populations have addressed the association between type 1 diabetes and HLA antigens. HLA class II alleles associated with type 1 diabetes were studied in 47 Zulu patients, and healthy blood donors were used as controls.<sup>20</sup> The HLA alleles associated with type 1 diabetes included HLA-DQB\*0302, DRB1\*09, DRB1\*04, DRB1\*0301, DQB\*0 and DQA\*03. Estimated haplotypes positively associated with type 1 diabetes included HLA DRB1\*0301-DQA\*0501, DRB1\*04-DQA\*03, DRB1\*04-DQB\*0302, DRB1\*0301-DQB\*0201, DQA\*0501-DQB\*0201 and DQA\*03-DQB\*0302. These findings were similar to those reported from Zimbabwe and other populations with type 1 diabetes.

## THE PATHOGENESIS OF TYPE 2 DIABETES AND THE METABOLIC SYNDROME

A panel of experts who met under the auspices of the WHO and International Diabetes Federation (IDF) in Colombo, Sri Lanka (IDF, 2002), concluded that genetics, foetal history, lifestyle and stress all contribute to the occurrence of type 2 diabetes.<sup>21</sup> The genetic contribution to its aetiology has not been studied adequately in black South Africans. The importance of family history in black South African patients with type 2 diabetes was investigated in Umtata.<sup>22</sup> Altogether 304 (27.3%) of 1 111 diabetic subjects reported at least one diabetic family member compared to 8.4% of control subjects. Of the subjects with a family history of diabetes, 87.8% had a first-degree relative with diabetes, 10.5% a second-degree relative and 5.9% a third-degree relative. Of those with a positive family history, 6.6% had a diabetic relative from both paternal and maternal sides, 31.1% from the paternal and 60.6% from the maternal side. Interestingly, patients with a positive family history had an earlier onset of diabetes than those without a family history (45 years vs. 52 years). The authors concluded that a strong genetic component for diabetes was found in Xhosa-speaking black South Africans, a finding that merits further and more detailed studies, as does the differential in maternal and paternal inheritance.

The relation between glucose tolerance and birth weight in black South African children was investigated in a group of 7-year-olds from the Birth-to-Ten (BTT) cohort.<sup>23</sup> The BTT is a prospective cohort study (n=3 170) of the determinants of growth, development and health in children born in the metropolitan area of Soweto and Johannesburg between April and June 1990. Glucose tolerance tests were carried out on 152 subjects at age 7 years. This was a subgroup randomly selected from 468 subjects with complete birth weight, height and weight data at 1 and 5 years. Inverse correlations were found between birth weight and insulin secretion during the first 30 min, as well as at 90 min, and between birth weight and the 30 min glucose concentrations. Children born with low birth weights but who, at the age of 7 years, were above the current median for weight had greater 120 min insulin concentrations. Children who could be at greatest risk of developing type 2 diabetes are those who have low birth weights and then gain weight rapidly by 7 years. Progressive beta-cell failure occurs in both black South Africans and African Americans with type 2 diabetes, but a major insulin-resistant variant also exists in African Americans which is not so for black South Africans.<sup>24</sup>

The metabolic consequences in early adult life of low birth weight were also investigated in a group of persons of mixed ancestry.<sup>25</sup> The association between low birth weight and glucose intolerance, blood pressure and dyslipidaemia was studied in 137 twenty-year-olds. They were the full-term offspring of primiparous women who delivered in the Groote Schuur Hospital maternal obstetric unit in 1976. They had either a low birth weight (< 10<sup>th</sup> centile for gestational age) or a normal birth weight (25<sup>th</sup> - 75<sup>th</sup> centiles). The low birth weight group had an 11.9% prevalence of glucose intolerance (IGT or diabetes) compared with 0% in the normal birth weight group. The former group had significantly higher systolic

blood pressures but no significant differences were seen in plasma triglycerides, cholesterol, and cholesterol sub-fraction concentrations, a finding that was somewhat unexpected. The investigators also examined the possible contribution of deranged functioning of the hypothalamic-pituitary-adrenal axis to the development of the metabolic syndrome in later life. ACTH stimulation tests were performed on a subset of both the underweight and control groups (n=32 and n=36, respectively). Nine am plasma cortisol concentrations as well as cortisol concentrations post-ACTH were significantly higher in the group who was underweight at birth than the normal birth weight group.

Huddle<sup>26</sup> recently audited the outcome of pregnancy in diabetic Sowetan women with a short-term natural history of gestational diabetes from 1992 - 2002. There were 348 women with gestational diabetes. Diabetes persisted in the immediate post-partum period in 29 and developed in one woman a year later. Almost half (46.5%, or 148 of 318) of the remaining women returned for an OGTT 6 weeks post-partum. At this stage, 20.3% had IGT and 20.3% had diabetes.

These data clearly demonstrate the substantial risk of GDM for the development of type 2 diabetes in South Africa. Furthermore, the post-partum period may serve as an opportunity to introduce strategies to reduce the prevalence of diabetes.

## THE METABOLIC SYNDROME

It has been known for some time that particular cardiovascular risk factors tend to cluster in the same individual more frequently than could be explained by chance alone.<sup>27,28</sup> This clustering of risk factors with glucose intolerance as a key feature has become known as the metabolic syndrome. The WHO in 1998 suggested the following working definition for the metabolic syndrome:<sup>1</sup> Glucose intolerance (IGT or diabetes) and/or insulin resistance together with two or more of the other components shown in Table 10.6. Several other components of the metabolic syndrome have been described (e.g. hyperuricaemia, coagulation disorders, raised PAI-1) but they are not necessary for the recognition of the condition.<sup>1</sup> The presence of the metabolic syndrome was associated with reduced survival, particularly because of increased cardiovascular mortality.<sup>1</sup>

Table 10.6. Other components of the metabolic syndrome

Impaired glucose regulation or diabetes
Insulin resistance (under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation)
Raised blood pressure $\geq 140/90$ mmHg
Raised plasma triglycerides ( $\geq 1.7$ mmol/L) <sup>1</sup> and/or low HDL-cholesterol $< 0.9$ mmol/L for men; $< 1.0$ mmol/L for women)
Central obesity (males: waist-to-hip ratio $> 0.90$ ; females: waist-to-hip ratio $> 0.85$ ) and/or BMI $> 30$ kg/m <sup>2</sup>
Microalbuminuria (urinary albumin excretion rate $\geq 20$ $\mu\text{g min}^{-1}$ or albumin:creatinine ratio $\geq 20$ mg g <sup>-1</sup> ).

A different set of criteria for the diagnosis of the metabolic syndrome was proposed by the National Cholesterol Education Program (NCEP)<sup>29</sup> in 2001 (Table 10.7).

Table 10.7. ATP III Definition of the metabolic syndrome

Risk factor	Defining level
Abdominal obesity	Waist circumference
Males	$> 102$ cm
Females	$> 88$ cm
Triglycerides	$> 1.7$ mmol/L
HDL-Cholesterol	
Males	$< 1.0$ mmol/L
Females	$< 1.3$ mmol/L
Blood pressure	$> 130/85$ mmHg
Fasting plasma glucose	5.6-7.0 mmol/L

The International Diabetes Foundation (IDF) have recently published new criteria for the metabolic syndrome (2005)

For a person to be defined as having the metabolic syndrome they must have:

Central obesity (defined as waist circumference  $\geq 94$  cm for European men and  $\geq 80$  cm for European women, with ethnicity-specific values for other groups)

Plus any two of the following four factors:

Raised TG level:  $\geq 150$  mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality

Reduced HDL-cholesterol:  $< 40$  mg/dL (1.03 mmol/L\*) in males and  $< 50$  mg/dL (1.29 mmol/L\*) in females, or specific treatment for this lipid abnormality

Raised blood pressure: systolic BP  $\geq 130$  or diastolic BP  $\geq 85$  mmHg, or treatment of previously diagnosed hypertension

Raised fasting plasma glucose (FPG)  $\geq 100$  mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

\* These values have been updated from those originally presented to ensure consistency with ATP III cut-points

The clustering of cardiovascular risk factors in adult black subjects in the Free State was such that 31% fulfilled the WHO criteria for the metabolic syndrome.<sup>30</sup> The impact of the metabolic syndrome, however, on this population still needs to be determined. Because of the common occurrence and possible clustering of the individual components of the metabolic syndrome in adults of both sexes and in all ethnic groups in South Africa, it is reasonable to conclude that the metabolic syndrome already has or will soon have a significant impact on cardiovascular disease morbidity and mortality in this country. The overall prevalence of the metabolic syndrome, as defined by the NCEP criteria in the US population was 23% in both sexes and was, lowest in black men (14%) and highest in Mexican-American women (27%).

The association between measures of obesity and other cardiovascular risk factors were studied in 124 treated black female hypertensive subjects.<sup>31</sup> The prevalence of the different components of the metabolic syndrome (WHO definition) was: BMI  $> 30$  kg/m<sup>2</sup> 66%, waist-to-hip ratio (WHR)  $> 0.9$  26%, IFG 13%, diabetes 9% and dyslipidaemia (fasting plasma triglycerides  $> 1.7$  mmol/L and/or HDL-cholesterol  $< 1.0$  mmol/L) 39%. Central obesity (waist circumference and WHR) was more strongly associated with fasting serum insulin, glucose, triglycerides, and uric acid than was BMI in this group of black hypertensive women.

Although the precise mechanisms that underlie the pathogenesis of the metabolic syndrome are unknown, the interaction between small birth size in full-term infants and subsequent growth patterns, in particular the development of obesity, is clearly an important process for the full expression of the chronic disease phenotype.<sup>32</sup> Attention should be given to reducing rates of childhood and adult obesity as well as seeking to minimize the recognised causes of low birth weight to prevent the emergence of the metabolic syndrome and the expected increase in numbers of subjects with type 2 diabetes in South Africa.

## MICROVASCULAR COMPLICATIONS OF DIABETES

Mortality and outcome was studied in a cohort of 64 young black patients with type 1 diabetes followed for 10 years in Soweto.<sup>33</sup> Twenty-four individuals from the original cohort of 88 were lost to follow-up. Ten of the 64 remaining patients died during the 10-year follow-up period. Renal failure was responsible for the majority of deaths (5/10), while three patients died of hypoglycaemia, and one each of diabetic ketoacidosis (DKA) and septic abortion. Thirty-six patients were available for clinical evaluation at baseline and after 10 years. Diabetic retinopathy was present in 52%, peripheral neuropathy in 42%, autonomic neuropathy in 47% and nephropathy in 28%. Six (17%) of patients had no complications.

Adequate routine screening for diabetic retinopathy remains a challenge at all levels of health care in South Africa. Screening for diabetic retinopathy with 60° retinal colour photography may offer a viable and cost-effective solution.<sup>34</sup> In 663 consecutive patients screened for diabetic retinopathy at the Johannesburg Hospital, retinal photography had a sensitivity of 93% and a specificity of 89% for any retinopathy, and 100% and 75%, respectively, for severe retinopathy, compared to an ophthalmologist's assessment. In this study the cost of screening in 1996 was R21 per patient screened, R49 per patient with retinopathy and R135 for each patient referred.

In a busy tertiary care setting the overall prevalence of diabetic retinopathy using 60° mydriatic retinal photography was 39%.<sup>35</sup> Severe diabetic retinopathy was present in 13% of patients and was more frequent in African and Indian patients compared to European ones. In this study, diabetic retinopathy was significantly associated with the duration of diabetes and with low levels of serum C-peptide, adjusted for glucose concentration. Severe degrees of retinopathy were associated with duration, African ethnicity, and macroalbuminuria. Poor diabetes control in these subjects, possibly because of

the infrequent prescription of insulin, may have been responsible for the increased prevalence of severe retinopathy.

A high prevalence of complications of diabetes in patients with suboptimal glycaemic and blood pressure control was found in 243 black African patients attending community health centres in Cape Town.<sup>36</sup> The mean duration of diabetes was 8 years and the mean HbA<sub>1c</sub> concentration of 10.5% reflected markedly sub-optimal diabetes control. Blood pressure control was satisfactory (SBP <140 mmHg and DBP <90 mmHg) in only 38.5% of patients taking anti-hypertensive medications. The prevalence of complications found in this study is shown in Table 10.4.

Table 10.8. Frequency of complications of diabetes in 243 black patients attending a community health care clinic in Cape Town

TYPE OF COMPLICATION	% (95% CI)
<b>FEET</b>	
Peripheral neuropathy	27.6 (15.2-39.9)
Peripheral vascular disease	8.2 (5.2-12.6)
Ulcers, sepsis, deformities	5.4 (2.1-8.7)
Amputation	1.4 (0.4-2.4)
Any foot problem	36.6 (23.3-50.0)
<b>EYES</b>	
Cataracts	
unilateral	6.2 (1.0-11.5)
bilateral	1.7 (0.0-3.4)
Retinopathy*	
background	35.4 (30.6-40.2)
proliferative	14.3 (7.9-20.7)
proliferative	4.3 (1.0-7.5)
Macular changes	13.1 (7.9-18.4)
Visual acuity	12.0 (8.8-15.3)
normal	53.2 (47.0-59.4)
bilateral moderate	12.0 (7.4-16.6)
unilateral mod/unilateral severe bilateral severe	9.2 (4.7-13.6)
<b>RENAL</b>	
Proteinuria	5.3 (2.5-8.1)
Elevated serum creatinine	5.9 (3.6-8.1)
Abnormal albumin:creatinine ratio	36.7 (29.0-44.4)

\* assessed by funduscopy by a trained general practitioner

A retrospective analysis of the clinical records of 219 patients (132 black, 87 Indian) with diabetes of more than 10 years duration conducted in King Edward VIII hospital, also showed a high prevalence of microvascular complications.<sup>37</sup> In this study 47 patients (36 blacks, 11 Indians) had type 1 diabetes and 172 (96 blacks, 76 Indians) had type 2 diabetes. The mean age of onset of type 1 diabetes was 24 years for black and 16 years for Indian patients. The mean age of onset for black and Indian patients with type 2 diabetes was 42 years and 38 years, respectively. In patients with type 1 diabetes the prevalence of retinopathy was 56% and 46%, respectively, for black and Indian patients, while persistent proteinuria was present in 25% of black and in 18% of Indian patients. Hypertension was present in 34% of both groups. In the group with type 2 diabetes, retinopathy was also more common in the black compared to the Indian patients (69% and 59%, respectively), as was hypertension (84% vs. 47%), while persistent proteinuria was more common in Indian compared to black patients (30% vs. 18%). The mean serum creatinine concentration too was higher in black patients (147 µmol/L) than in Indian patients (113 µmol/L).

The frequency of diabetic retinopathy and nephropathy was studied in 30 patients with pancreatic diabetes matched with 30 patients with type 1 diabetes.<sup>38</sup> The prevalence of retinopathy was very similar in the two groups (33% of patients with pancreatic diabetes and in 40% of patients with type 1 diabetes). The spectrum of disease was also very similar in the two groups. The prevalence of microalbuminuria (33%) was also identical in the two groups. This data contradict the notion that microvascular complications are rare in patients with chronic pancreatitis.

Diabetic neuropathy was detected in 26% of female patients attending a primary health-care clinic in Mamelodi by utilising a nylon monofilament.<sup>39</sup> This technique was superior to pinprick and cotton wool to detect neuropathy while fair agreement was found between 10 sites and 3 sites tested with the monofilament.

The high prevalence of microvascular complications in patients with diabetes is of considerable concern as these are preventable or at least modifiable with good glycaemic and blood pressure control. Furthermore, as there is such restricted access for public sector patients with diabetic end-stage renal disease to dialysis or transplantation in South Africa because of severely limited resource allocation, the emphasis needs to be placed on prevention.<sup>40</sup> A greater demand for renal replacement therapy is expected because of a projected rise in diabetes prevalence.

In a study performed at Hlabisa district hospital, 253 Zulu patients with diabetes were evaluated for diabetes control and the presence of complications.<sup>41</sup> The mean age of the subjects was 56.5 years and the mean duration of diabetes after diagnosis 4.2 years (6 week to 60 years). Seven percent were classified as having type 1 diabetes and the remainder had type 2. The mean HbA1c concentration was 11.3%. Hypertension was present in 65% of patients and a target blood pressure of <130/85 mmHg was only achieved in 20% of them. Diabetic retinopathy was present in 40% of patients and an elevated albumin:creatinine ratio was found in 46%, while overt proteinuria was present in 13%. Foot pulses were absent in 17% of patients and foot ulceration was present in 6%. A history consistent with stroke was elicited from 8% of patients.

## MACROVASCULAR COMPLICATIONS

There is not a great deal of recent data on the frequency of macrovascular complications in South African diabetic patients. A study conducted in Johannesburg indicated that the frequency of dyslipidaemia did not differ between two groups of black patients with type 2 diabetes, one with a higher and one with a lower socio-economic level, despite significantly worse diabetes control in the latter.<sup>42</sup> Serum triglyceride levels, however, were significantly increased in males from the higher socio-economic group. Interestingly, in female patients with type 2 diabetes from the lower socio-economic group, mean total serum cholesterol concentration increased from 4.8 mmol/L in 1976 to 5.3 mmol/L two decades later, while serum triglyceride levels did not change significantly.

Some of the problems regarding vascular evaluation in patients with diabetes were highlighted in a study of 85 black female patients attending a Mamelodi diabetes clinic.<sup>43</sup> None of the patients who had intermittent claudication according to the Rose questionnaire had both pedal pulses absent on the affected side. There was also a low prevalence of medial arterial calcification (10%) and this did not correlate with the ankle brachial index >1.3. This study showed good agreement between ankle brachial index and toe brachial index if the ankle brachial index was <1.3. The authors also found a good correlation between lower ankle brachial index and absence of both pulses in the foot suggesting these patients may benefit from more extensive work-up.

Although smoking is common among black patients with diabetes (20% compared to 28% in the general population),<sup>44</sup> macrovascular complications were absent in a cohort of 36 patients with type 1 diabetes followed for 10 years.<sup>45</sup>

The association of known cardiovascular disease risk factors with acute myocardial infarction in sub-Saharan Africa was explored in the Interheart study. This was a case-control study of patients with a known first myocardial infarction and is the longest of its kind in the region. Five risk factors – smoking, history of diabetes, history of hypertension, abdominal obesity and Apo B: Apo A1 ratio accounted for 89.2% of the population attributable risk (PAR) for acute MI in the overall African population and an 87.7 PAR in the black African participants. The strongest individual risk factors in the overall African population with diabetes (OR 3.55, 95% CI 2.53, 4.99) and hypertension (OR 3.44, 95% CI 2.64, 4.48) were similar to the overall international Interheart study. These data clearly indicate that diabetes is a major contributor to myocardial infarction in all ethnic groups in sub-Saharan Africa.<sup>46</sup>

## ACUTE DIABETES COMPLICATIONS

Hyperglycaemic emergencies remain an important cause for the hospital admission of diabetic patients in South Africa.<sup>47</sup> Hyperglycaemic emergencies were responsible for 23.5% of the annual diabetes related admissions (n=614). Diabetic ketoacidosis (DKA) was the most frequent diagnosis (19.2%), particularly among the black African patients. A striking phenomenon was that 55% of patients fulfilling the criteria for DKA had type 2 diabetes. Severe infection along with relative insulinopaenia in African patients with diabetes was postulated to be responsible for this phenomenon. The overall mortality in the hyperglycaemic group was 5.5%, comparable to most western societies.

A study of 122 patients admitted to Groote Schuur Hospital over a 4-month period with 131 hyperglycaemic emergencies found that a smaller proportion with mild or severe DKA had type 2 diabetes. The predominant precipitating causes for admission were infections (47%) and non-compliance

with therapy (26%). The mortality rate in this study varied according to category of emergency. It was 3% in mild DKA, 11% in severe DKA and 19% in the hyperosmolar non-ketotic group.

In conclusion, in South Africa, a number of epidemiological questions remain. These include

1. Has there been a true increase in type 2 diabetes over the past decade, and, if so, what is the extent of the rise?
2. What is the extent of the rural-urban difference in diabetes prevalence?
3. What is the incidence of type 1 diabetes?
4. What are the health-care costs of diabetes?
5. What is the extent of the burden of diabetic complications, e.g. blindness and amputations?

The following studies would go some way to answer these questions:

- Examining the current prevalence of type 2 diabetes among rural and urban communities, ideally on a national basis.
- Initiating national type 1 diabetes registers to facilitate studies on the incidence, morbidity and mortality of this group of individuals.
- Initiating cohort studies to determine the natural history of diabetes and its complications in other countries.

This chapter has focused on the epidemiology of diabetes and its complications. It has not attempted to address any aspect of diabetes health-care research or management of diabetes as this is included in Chapter 17.

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