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REVIEW

A sub-Saharan African perspective of diabetes

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Abstract Diabetes mellitus is an important and increasing cause of morbidity and mortality in sub-Saharan Africa. Accurate epidemiological studies are often logistically and financially difficult, but processes of rural–urban migration and epidemiological transition are certainly increasing the prevalence of type 2 diabetes. Type 1 disease is relatively rare, although this may be related to high mortality. This diabetic subgroup appears to present at a later age (by about a decade) than in Western countries. Variant forms of diabetes are also described in the continent; notably 'atypical, ketosis-prone' diabetes, and malnutrition-related diabetes mellitus. These types sometimes make the distinction between type 1 and type 2 diabetes difficult. Interestingly, this is also a current experience in the developed world. As more detailed and reliable complication studies emerge, it is increasingly apparent that African diabetes is associated with a high complication burden, which is both difficult to treat and prevent. More optimistically, a number of intervention studies and twinning projects are showing real benefits in varying locations. Future improvements depend on practical and sustainable support, coupled with local acceptance of diabetes as a major threat to the future health and quality of life of sub-Saharan Africans.

Keywords Africa · Atypical diabetes · Diabetes mellitus · Diabetic complications · Healthcare delivery · Malnutrition-related diabetes mellitus · Mortality · Type 1 diabetes · Type 2 diabetes

Abbreviations

CAD	coronary artery disease
FCPD	fibrocalculous pancreatic diabetes
GADA	GAD antibodies
HNK	hyperosmolar non-ketotic coma
ICA	islet cell antibodies
IDF	International Diabetes Federation
MMDM	malnutrition-modulated diabetes mellitus
MRDM	malnutrition-related diabetes mellitus

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Introduction

Diabetes mellitus in the African continent is hugely affected by epidemiological factors and issues of healthcare economics. A major factor increasing diabetes prevalence in Africa is urbanisation [1]. There continues to be an increasing number of people moving into urban areas from rural environments, particularly in sub-Saharan Africa. This migration is inevitably associated with a shift in lifestyle from a relatively healthy traditional pattern, to the urban scenario of increased food quantity and reduced quality, low levels of exercise, smoking and increased alcohol availability [2]. This rapid and dramatic epidemiological

transition is driving the emergence of high and increasing prevalence rates of type 2 diabetes and hypertension [3], with growing mortality implications. Indeed, even though at present infective diseases such as HIV infection, tuberculosis and malaria dominate mortality in sub-Saharan Africa, it is predicted that by 2020, non-communicable diseases will proportionately overtake infections as the major cause of mortality [4]. The burden of non-communicable diseases in Africa is already proportionately greater than that in Western countries [5].

As well as quantitative issues, diabetes epidemiology in Africa also involves a number of qualitative peculiarities. Type 1 disease appears rarer than in Western countries [6], and 'malnutrition-related' and 'atypical' forms of type 2 diabetes have been described. With the migration of many African people to Europe and America, some of these unusual diabetic subgroups may now be seen in developed countries. Indeed, a recent study of atypical type 2 diabetes (discussed later) has used a cohort of African patients now resident in France [7].

The diabetes care delivery agenda in Africa is dominated by poverty, especially in sub-Saharan Africa, where 33 out of the 40 (82%) of the world's most heavily indebted poor countries are situated [8]. Also, in the African continent, diabetes management costs have to compete with health issues such as anti-retroviral drugs, tuberculosis treatment and malarial control programmes. As a continent heavily dependent on the developed world for aid, it is important that health problems in Africa are understood by the rest of the world. Diabetes is a good example, as the epidemiology of this disease and care systems in place for its treatment are very different in Africa from those in Western countries. In this article, we will try to emphasise unique perspectives of diabetes in sub-Saharan Africa, as well as aspects that can perhaps provide lessons elsewhere.

Problems of numbers, classification and diagnosis

As observed elsewhere in the world, the majority of diabetic patients in Africa have type 2 disease. Drawing information from the separate African continent, the International Diabetes Federation (IDF) estimates a current overall prevalence of 2.4% [9]. Good epidemiological studies are difficult in sub-Saharan Africa; they are expensive, labour intensive and populations are often mobile and poorly enumerated. Figure 1 shows a map of the area with recent adult diabetes prevalence estimates by country. The figures are from cohort studies (using glucose tolerance tests) and derived projected data from known population structure (rural/urban distribution and age). It was compiled by the IDF in 2003 (included in [9, 10]). Generally speaking, prevalence is significantly higher in urban compared with rural communities, and is particularly high in particular ethnic groups, notably the descendants of Asian migrants. As well as these epidemiological issues, there are classification difficulties in Africa (see Textbox: Epidemiological issues in African diabetes), discussed below.

Epidemiological issues in African diabetes

- Overall prevalence 2–3%, but wide variation. Higher rates in:
  –urban areas
  –Asian immigrants
  –North Africa
- Low incidence of type 1 diabetes
- Malnutrition-related diabetes
- Atypical 'ketosis-prone' diabetes

Atypical African diabetes An atypical presentation of diabetes was first described in the late 1960s by researchers working in Africa [11–16]. Subsequent reports from Nigeria described patients who could switch from insulin therapy to oral hypoglycaemic agents or vice versa [15, 16], as well as those with ketoacidosis but without islet cell antibodies (ICA) [13, 14]. In 1985, Ahren and Corrigan [12], working in northern Tanzania, described this atypical diabetes with phasic insulin-requiring profiles in the absence of obvious precipitating factors for ketosis. It has now become apparent that there are other forms of atypical presentations of diabetes, with predominance in populations of African ancestry that do not easily fit the criteria defining the main known types. The most often reported atypical form of diabetes is characterised by an initial clinical presentation of apparent type 1 diabetes with severe hyperglycaemia and ketosis, and subsequent long-term remission with or without relapses or a clinical course compatible with type 2 diabetes.

The term 'ketosis-prone atypical diabetes mellitus' was first described in African-American children in 1987 [17, 18]. The first reports of well-phenotyped African-American adults came from New York in 1990 and 1994, in which 'Flatbush' diabetes, with the same characteristics as ketosis-prone atypical diabetes, was described [19, 20]. Unlike patients with true young-onset type 1 diabetes [20], both the GAD antibodies (GADA) and ICA are an exceptional finding in patients with this form of acute-onset ketotic diabetes [14, 20–22]. A syndrome similar or identical to the US descriptions has been described more recently in West Africa [23]. Children presenting with atypical diabetes are mostly African or of African ancestry, obese, have an age of onset around 14 years and a strong positive family history of type 2 diabetes approaching 100%; there is a male preponderance of up to 3:1 [17, 18, 21, 23]. The age at diagnosis in

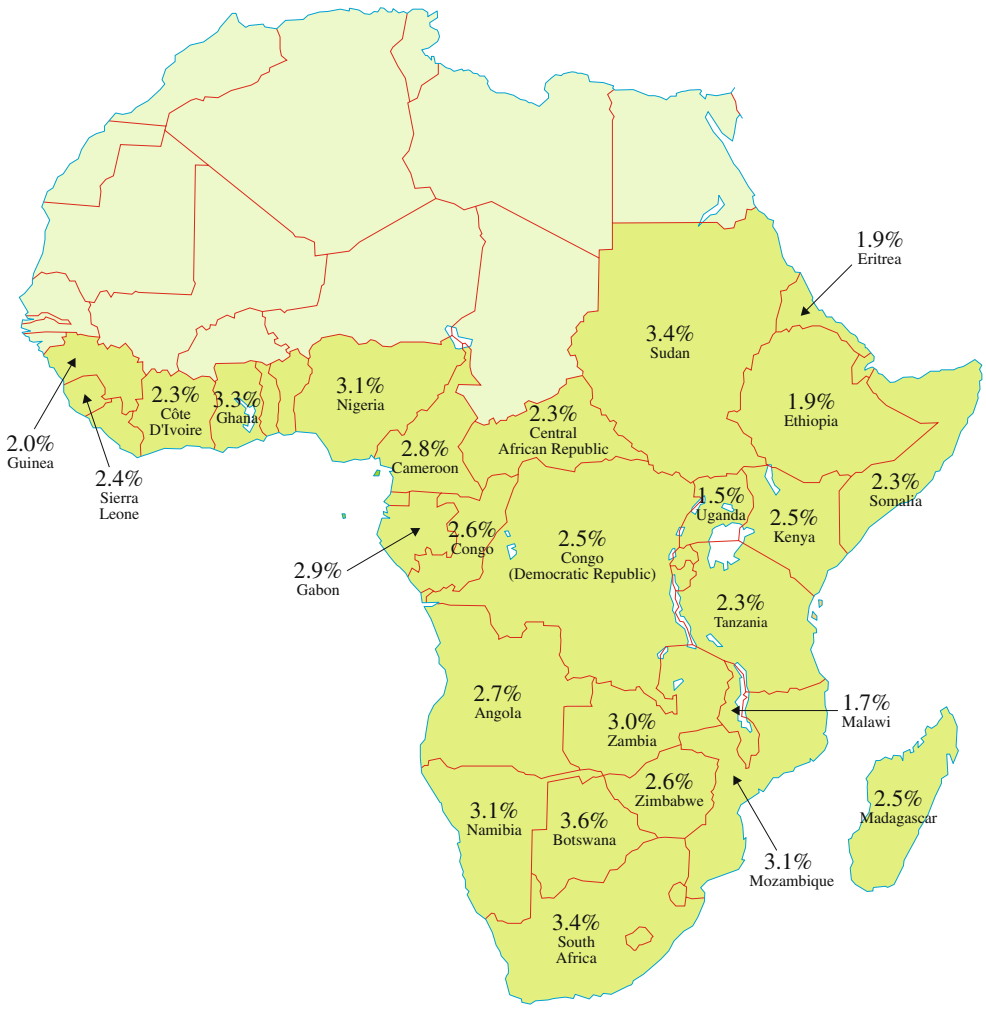

Fig. 1 Map of Africa showing estimated adult prevalence rates in different countries. Darker shading indicates sub-Saharan countries. Localised areas of much higher prevalence also exist, e.g. 10.8% in the 'Cape-coloured' population of Capetown, South Africa; and 9.8% among Asian immigrant descendants in Dar es Salaam, Tanzania. (IDF figures, 2003, adapted from [9, 10])

adults varies from 35 to 46 years. Adults with atypical diabetes are less often obese than children (depending on the population studied, obesity is present in not more than 56%). The initial presentation is usually acute with polyuria, polydipsia and weight loss. The result of a random blood glucose test is very high (often above 30 mmol/l), ketones are present in the urine and there may be ketoacidosis with low pH and serum bicarbonate [12, 17, 22, 24]. Thus, the initial presentation requires insulin treatment with appropriate fluid and electrolyte management as necessary. A recent interesting and exciting development in the aetiology of ketosis-prone atypical diabetes has come from work by Sobngwi et al. [7]. Antibodies to the human herpesvirus 8 (HHV-8) were found in 88% of patients with atypical diabetes but in only 15% of patients with classical type 2 diabetes ($p<0.001$). This may explain the abrupt onset of the disease and its subsequent benign clinical course, sometimes with glycaemic remission.

Malnutrition-related diabetes mellitus This syndrome was previously known as 'tropical diabetes' or 'tropical pancreatic diabetes' and is characterised by early-onset non-ketotic diabetes in underweight patients, with very high subsequent insulin requirements [25]. The acute onset with very high glycaemic levels, and sometimes ketosis or ketoacidosis is compatible with type 1 diabetes, but the non-insulin dependent clinical course is more likely to mimic type 2 diabetes. This atypical presentation is distinct from true African type 1 diabetes with regard to beta cell autoimmunity [26]. Although the HLA alleles associated with susceptibility to type 1 diabetes are of high frequency in some populations with this form of diabetes [20], there is an absence of markers of pancreatic beta cell autoimmunity [17]. Patients with malnutrition-related diabetes mellitus (MRDM) have been described in geographically distinct areas throughout the tropics, including Africa, and a male predominance has been described (as with atypical diabetes) [27]. Pancreatic calcification is sometimes present (so-called fibrocalculous pancreatic diabetes or FCPD). Without this feature it is known as malnutrition-modulated diabetes mellitus (MMDM). As both names suggest, present or past malnutrition is a feature, although it is uncertain whether this may be causative, or secondary to uncontrolled diabetes and/or exocrine pancreatic deficiency. The nature and even

existence of MMDM is, however, uncertain and controversial. Fifteen years ago, the well-known Kenyan diabetologist Tom Johnson described it as 'a syndrome seeking clarity' [28], and the same is very much true today. Because of these problems of definition, there are no reliable data on the relative frequency of MRDM (and indeed atypical diabetes). Table 1 summarises the key features of these two diabetes variants.

Type 1 diabetes In Africa, the presence of atypical forms of diabetes makes it difficult to classify patients as having type 1 and type 2 diabetes based on usual clinical criteria [29–32]. Interestingly, there is currently debate in Europe over whether type 1 and type 2 diabetes may share some common aetiologies—the so-called accelerator hypothesis [33, 34]. The difficulty in classifying and diagnosing some forms of diabetes in Africa may explain why approximately half (42–64%) of African patients initially treated with insulin do not have classical type 1 diabetes and may enter prolonged remission [30, 35]. It is widely believed that classical type 1 diabetes is less common in Africa than in Europe or North America, and this is certainly common clinical experience. However, early out-of-hospital mortality may confound this impression, and the question remains open. Epidemiological studies of type 1 diabetes are few and are difficult to conduct because of problems in finding cases as well as enumeration of the background population. Incidence rates of 10 per 100,000 per year have been reported from Sudan [36], and 1.5 per 100,000 per year from Tanzania [37]. Both are certainly lower than expected Western rates. One interesting and unexplained feature of African type 1 diabetes is that the age of onset is about 10 years later than elsewhere. In a unique study from Johannesburg, South Africa, it was found that the mean age of presentation was 23 years for black African type 1 patients compared with 13 years for white African type 1 patients [38]. This contrasts with the falling age of onset of type 1 diabetes in Europe [39]. Immunological studies in black African patients with clinically diagnosed type 1 diabetes have been hampered by cohorts with varying disease duration and variable and sometimes dated laboratory methodology. Early studies reported low rates of ICA positivity [40, 41]. More recently, 44% of recently diagnosed (within 1 year of presentation) black South African type 1 patients were found to be GADA-positive [42]. A further study from South Africa measured GADA in 43 black and 17 white type 1 patients presenting in ketoacidosis. The rate of GADA positivity was 32% in black and 67% in white patients ($p=0.03$) [43], although diabetes duration was not exactly matched. Results such as these have led some workers to surmise that non-autoimmune factors may be a major determinant of type 1 diabetes in black sub-Saharan Africans [8].

Table 1 Summarised features of 'atypical' and 'malnutrition-related diabetes' in Africa

Atypical	Malnutrition-related
Ketotic presentation	Insidious onset
Children or young adults	Young adults
3:1 Male excess	2:1 Male excess
Islet autoimmunity rare	Occasional 'type 1' HLA pattern
Often strong family history	Past or present malnutrition
Remission possible	Steatorrhoea in some areas

Other diagnostic and classification issues The clinical combination of weight loss, polyuria and sepsis has led to the erroneous diagnosis of AIDS in diabetic patients, and contributed to the delay in seeking medical care in Africa, where HIV/AIDS is now endemic [44]. Now that antiretroviral drugs are being widely used in African patients with AIDS, the metabolic syndrome and type 2 diabetes may soon occur as an adverse effect. Furthermore, there are socioeconomic inequalities in health that can be attributed to inadequate access to healthcare and other inequalities in material circumstances. These are intermediate factors that may lead to a misdiagnosis or a delay in diagnosis of diabetes. Cultural factors and health beliefs differ in sub-Saharan Africa, where under-nutrition and opulence coexist; food remains a daily challenge and overweight can be subsequently perceived as a sign of wealth. Indeed, being obese is a deeply rooted status symbol. Obviously, there are wide geographical variations in these perceptions, in addition to differences between urban and rural environments. However, in a continent where there is an underdeveloped healthcare system with poor diagnostic facilities, and where poverty can be considered a disease, the atypical presentations of diabetes, health beliefs and the endemic HIV/AIDS epidemic can lead to difficulties in the classification and diagnosis of diabetes.

Complications and mortality

Chronic complications It was traditionally thought that chronic complications of diabetes are rarely seen in Africa as a consequence of the high mortality rate leading to a low mean disease duration in most patients. Although there is some truth in this, there is no doubt that if carefully looked for, chronic diabetic complications are not infrequently seen. Thus, the prevalence of retinopathy has been recorded as 7–52%; cataract, 9–16%; neuropathy, 6–47%; nephropathy, 6–30%; and macroangiopathy, 1–5% [45, 46]. Table 2 summarises the recent complication prevalence studies in various parts of Africa. For each of the complications of retinopathy, neuropathy, nephropathy and microalbuminuria,

Table 2 Selected chronic complication prevalence studies of diabetes in Africa

Complication	Location	Year	Prevalence (%)
Retinopathy			
[47]	Cape Town	1997	55
[48]	Nigeria and Ghana	2003	18
Nephropathy			
[49]	Egypt	2004	14
[50]	Nigeria	2003	28
Neuropathy			
[51]	Tanzania	2000	25
[52]	Libya	1999	46
Microalbuminuria			
[53]	Tanzania	2007	11
[54]	Cameroon	1999	53

two separate studies are quoted [47–54]. The important points from these studies are that the specific complications of diabetes are common in the African continent, but their quoted prevalence varies enormously. This is almost certainly related to wide variations amongst the populations studied, including diabetes duration, glycaemic control, other risk factors (e.g. hypertension, smoking), population studied (hospital or community), diagnostic facilities and possibly ethnic factors.

The relatively high frequency of neuropathy leads, as may be expected, to a significant problem of foot ulceration [55]. The majority of diabetes-related foot ulcers (>80%) in Africa are neuropathic rather than ischaemic, presentation may be late and the outcome often poor [56]. A further problem is that in many African societies there are strong cultural objections to amputation—loss of a limb may be considered worse than loss of life [55]. Diabetes-related large vessel disease syndromes are generally less common than in developed countries (particularly in sub-Saharan areas of the continent) [57]. Following detailed studies in the Copperbelt of Zambia, Rolfe found only 12 out of 600 participants had possible coronary artery disease (CAD; according to ECG diagnosis only), seven had past strokes and ten had peripheral vascular disease [58]. It was calculated that large vessel disease was uncommon, in spite of the high prevalence of hypertension. Similar observations were made at around the same time in Ethiopia, where Lester and Keen reported that macrovascular disease was not common among middle-aged Ethiopian diabetic patients [59]. Even in 2000, definite CAD was considered rare enough among Nigerian diabetic patients for two cases to be reported in the literature [60].

Acute complications The acute metabolic complications of diabetic ketoacidosis, hyperosmolar non-ketotic coma and hypoglycaemia all commonly occur in Africa, and have a worse prognosis than in developed countries. Severe diabetes-related infections can also perhaps be considered an acute complication of the disease. Diabetic ketoacidosis may have a mortality rate of 10–30% [9, 61], and is often due to a lack of insulin or delayed presentation (related to both the patient attending traditional healers initially, but also to misdiagnosis when attending clinics or hospitals) [62]. One of the few outcome studies of hyperosmolar non-ketotic coma in Africa was from Johannesburg, South Africa, and reported a mortality rate of 41% [63]. Hypoglycaemia as a cause of hospital admission is more frequently related to sulfonylurea drugs (33% of hypoglycaemic admissions in one study) [64] than in developed countries, and such hypoglycaemia may be severe and prolonged. Acute diabetes-related infections include foot sepsis of course, but also unusual problems such as severe hand infections [65] and, occasionally, mucormycosis. Tuberculosis is also more common and more severe in patients with diabetes [66].

Metabolic and infective complications have been the major reasons for the high excess mortality associated with diabetes in Africa. Over a hundred years ago, the British missionary doctor in Uganda, Albert Cook, recorded that diabetes was ‘very fatal’ [67]. Sadly, this remains the case, although there is some evidence of improvements in at least some locations over the last 10–20 years. Population mobility, patient tracing and mortality enumeration all make it difficult to conduct reliable outcome studies in Africa. The main reports are summarised in Table 3 [68–71]. The landmark initial study was by Castle and Wicks in Harare, Zimbabwe, some 30 years ago. They carefully followed a mixed-type cohort of 97 diabetic patients admitted to hospital [68]. With a high level of case tracing, they found that 6 years later, 41% had died—nearly all from metabolic or infective causes. They identified male sex, alcohol abuse and insulin treatment as being particular risk factors. In 1990, McLarty and colleagues from Dar es Salaam, Tanzania, reported on a larger series (again of mixed type) followed between 1981 and 1987 [69]. This was not a single cohort followed from one time point, but calculated 5 year mortality rates showed 66% survival if on insulin, and 82% if on oral agents. The increased risk conferred by insulin treatment described a decade earlier by Castle and Wicks [68] was thus again confirmed, although the overall outcome figures were a little improved. However, compared with European figures, the Tanzanian data was still depressing—McLarty et al. [69] showed that 5 years from presentation, one-third of those on insulin are likely to have died, whereas in Europe, 40% of such patients should survive for 40 years or more [72]. The increased mortality risk associated with insulin treatment may reflect dangers of insulin treatment itself (particularly without self-monitoring of blood glucose), or it may simply reflect that this represents a high-risk diabetic subgroup.

In Soweto, South Africa, a long-term follow-up of a type 1 cohort reported mortality rates at 10 [70] and 20 [71] years

Table 3 Diabetes mortality studies in Africa

Country	Year	Diabetes types	Outcome	Mortality causes
Zimbabwe [68]	1980	Mixed—most type 2	41% had died at the 6-year follow-up	Most due to DKA, HNK, hypoglycaemia and infection
Tanzania [69]	1990	Mixed—most type 2	5-year mortality: 18% if not on insulin; 34% on insulin	Metabolic and infections. Some cardiovascular causes in type 2 patients
South Africa [70, 71]	1995, 2005	All type 1	Mortality rate16% at 10 years, 43% at 20 years	About half of deaths were nephropathic, others were due to DKA and hypoglycaemia

DKA, diabetic ketoacidosis; HNK, hyperosmolar non-ketotic coma

from recruitment. There were originally 88 in the cohort, all with definite type 1 disease (confirmed by C-peptide testing), followed from 1982. At the 10-year follow-up (1992) [70], 16% had died; half of the deaths were due to nephropathy and the rest due to diabetic ketoacidosis or hypoglycaemia. At 20 years, the crude mortality rate was 43% [71], with a Kaplan–Meier calculated mortality hazard rate of 33%. Renal failure owing to nephropathy was again the main mortality cause (43%). Other causes were hypoglycaemia (29%), diabetic ketoacidosis (10%) and infection (10%). Although the overall 20-year mortality figures were in excess of those reported in developed countries, interestingly, they were similar to figures from equivalent Afro-Caribbean type 1 patients in the USA [72].

Overall, the outcome of African diabetes remains poor, but there is evidence of improvement in the recent past. Metabolic and infective causes of death remain important, but nephropathic renal failure is an increasing problem. Large vessel disease syndromes as causes of mortality are also probably emerging [69, 73].

Delivering care: existing problems and potential solutions

Economic factors remain an important barrier to adequate diabetes care delivery in Africa. Insulin, in particular, is a relatively expensive drug in resource-limited countries. In 1992, in Tanzania, Chale et al. [74] calculated that those in the country on insulin treatment (0.2%) were consuming 8% of the national healthcare budget. This well-known chronic 'insulin dilemma' has been revisited in detail by Beran and colleagues of the International Insulin Foundation [75, 76]. They have carried out in-depth studies of the insulin supply problem in specific African countries, using a newly introduced Rapid Assessment Protocol for Insulin Access (RAPIA) system of enquiry, operating at various levels, from health ministry to patient. Problems identified included poor quantification of need, high insulin cost, erratic peripheral delivery and, sometimes, failure to take advantage of cheaper insulin alternatives.

Diabetes is perhaps the index case of a general problem of non-communicable disease healthcare delivery in developing countries.

Problems and barriers identified by WHO [8]

- Lack of organisational structure for chronic disease care
- Minimal staffing and training provided to healthcare workers in the field, and a lack of resources
- Minimal communication with the public to address preventative strategies
- Non-existence of organised healthcare information systems
- Lack of involvement and integration with other community resources

Chronic disease care is compounded with the higher political priorities of infective diseases, poor supply of drugs and monitoring equipment and, for many people, a reliance on traditional rather than Western medicines [77–79].

Care inadequacies particularly in relation to diabetes, as identified by Whiting et al. [78]

- Poor patient attendance at clinics
- Because of the low doctor:patient ratio, short consultation times and limited or no time for educating patients
- A lack of evaluation and monitoring for the complications of diabetes
- Non-existent or inadequate referral systems
- Poor organisation of services
- Poor record keeping/information technology
- Lack of infrastructure to support services
- Unaffordable medicines and other resources
- Inequality in the distribution of healthcare facilities
- Non-existent diabetes multidisciplinary healthcare teams
- Lack of national policies

There have been scattered reports of successful attempts to improve diabetes care delivery and outcome, but sadly these have largely been initiated either by local hospitals or by external funding and support. In Soweto, during the 1980s, hyperglycaemic emergency admission rates and mortality were reduced by a package of measures, which included patient and staff education and formalised treatment protocols [80]. A team-based restructuring of care in Ghana, including, in particular, nurse-led patient education, resulted in reduced diabetes-related admission rates and inpatient mortality [81]. Both of these studies were from city teaching hospitals, and the Soweto project was internally organised and cost-neutral. The Ghana initiative was aided by an external non-governmental organisation, namely, the Tropical Health and Education Trust (THET). This trust has also been active in the Jimura area of Ethiopia, promoting a devolved system of non-communicable disease (including diabetes) care in rural health centres [82]. Although this has proved highly successful, hard outcome indicators have not been assessed, and high levels of staff turnover have been a problem. In rural KwaZulu-Natal in South Africa, a previous successful non-communicable disease delivery programme [83] has been used as the basis for a nurse-only approach to deliver protocol-based diabetes care and structured patient education to a scattered community at the primary health clinic level [84]. Significant falls in glycated haemoglobin (HbA_{1c}) levels were seen over 18 months of follow-up. This project was supported by the Rhodes Trust and the Liverpool School of Tropical Medicine, but is currently self-sustaining [85]. Finally, in Eritrea [86], a US team made three visits to the country over a 2-year period to support and educate local diabetes health workers. A subsequent significant fall in mean patient HbA_{1c} levels was demonstrated. The project was funded by the USA, and although clearly of value, there are issues concerning long-term sustainability. As well as those evidence-based interventions, there are a number of other support projects and initiatives ongoing in the continent. These include a twinning project between Diabetes UK and the Mozambique Diabetes Association, and the introduction of a National Diabetes Programme in Tanzania [87].

The lessons appear to be that real improvements in diabetes care and outcome in Africa are achievable. However, although external support, local health facilities, support groups and diabetes associations all have a role to play, national government health departments need to take the responsibility of instigating widespread permanent change and improvement. The costs need not be great, as patient education (one of the least expensive of diabetes treatments) has been shown to be a major and effective part of all the currently described care delivery packages [80–86]. The integration of traditional healers should also be considered as part of these reforms, since, to the everyday African, they are very much a part of illness management.

The complication and mortality burden of diabetes in Africa is high and increasing. With increasing urbanisation and transitional lifestyles, CAD and the metabolic syndrome are now significantly emerging problems [88] that require urgent attention. In 1977, Morley et al. [89] from Baragwanath Hospital in Soweto, South Africa, wrote, ‘we do not underestimate the difficulties of providing a proper service for diabetics, but we should be able to do better’. Over 30 years later, one would have to conclude that more should have been achieved.

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