Pathogenesis of type 1 and type 2 diabetes mellitus in sub-Saharan Africa: implications for transitional populations

Kwame Osei[a], Dara P. Schuster[a], Albert G. B. Amoah[b] and Samuel K. Owusu[b]

The increasing prevalence and incidence of diabetes and its long-term complications in sub-Saharan Africa (SSA) could have devastating human and economic toll if the trends remain unabated in the future. Approximately 90% or majority of patients with diabetes belongs to the adult onset, type 2 diabetes category while 10% have type 1 diabetes in SSA. However, because of the paucity of metabolic and clinical data, a clear understanding of the natural history of both diseases and the classification of diabetes subtypes has been hampered. Nevertheless, we have attempted to provide a concise review of the pathophysiology of both type 1 and type 2 diabetes as well as phenotypic and clinical variations in patients residing in SSA. The limited metabolic data, (albeit increasing), from high-risk and diabetic individuals in the SSA, have contributed significantly to the understanding of the pathogenetic mechanisms of diabetes and the variations in the presentation of the disease. Sub-Saharan African patients with type 1 diabetes have essentially absolute insulin deficiency. In addition, patients with type 2 diabetes in SSA region also manifest severe insulin deficiency with varying degrees of insulin resistance. Although the exact genetic markers of both diseases are unknown, we believe studies in patients of SSA origin who reside in diverse geographic environments (African diaspora) could potentially contribute to our understanding of the genetic and environmental mediators of both diseases. However, many intrinsic, individual and societal obstacles such as poor education and illiteracy, low socio-economic status and lack of access to health care make uncertain the translation of diabetes research in SSA. In this regard, effective management and/or prevention of diabetes in SSA individuals should adopt multidisciplinary approaches. Finally, innovative health care delivery and educational models will be needed to manage diabetes and its long-term complications in SSA. *J Cardiovasc Risk* 10:85–96

Journal of Cardiovascular Risk 2003, **10**:85–96

Key words: type 1 diabetes, type 2 diabetes, beta-cell function, insulin resistance, sub-Saharan Africa

[a]The Ohio State University College of Medicine and Public Health, Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Ohio, USA and [b]Korle Bu Teaching Hospital University of Ghana Medical Korle-Bu, Accra, Ghana.

Correspondence and requests for reprints to Kwame Osei MD, FACE, FACP, 491 McCampbell Hall, 1581 Dodd Drive, Columbus, Ohio 43210, USA.
Tel: 614 292 5201; fax: 614 292 1550;
e-mail: osei-1@medctr.osu.edu.

Introduction

Diabetes has reached epidemic proportions in several populations [1–4]. The majority of these patients reside in developing countries [1–3]. Approximately 90% or the majority of patients with diabetes belong to the adult onset, type 2 diabetes category and 10%, type 1 diabetes. Until recently, type 1 diabetes was reported to be uncommon in people of sub-Saharan African (SSA) regions [5–8]. While this could be true decades ago, there was lack of accurate ascertainment of diagnosis in these indigenous black African populations. In sub-Saharan Africans, most children and adolescents with type 1 diabetes who do not have access to basic health care facilities and insulin are more likely to succumb to the disease within the first year after diagnosis. Similar to type 1 diabetes, type 2 diabetes was also uncommon in SSA with a prevalence rate of less than 0.5% in most populations approximately three decades ago [1–12]. However, type 2 diabetes and the associated long-term complications continue to accelerate exponentially in most of the SSA regions and in Blacks of African ancestry [1–3,13–24].

Many intrinsic, individual obstacles, such as poor education, illiteracy and lack of family support, make the translation of diabetes and its associated complications major challenges for the patients, family members and the health care providers. Levetan *et al.* [17] have determined factors associated with diabetic hyperglycaemic emergencies in Cape Town. Poor education, low socio-economic status and lack of insulin were the greatest culprits. Swai *et al.* [5,11] found similar factors to account for the high mortality in newly diagnosed type 1 and 2 diabetic patients. Levetan *et al.* [17] further reported that the mortality of diabetes in acute care hospitals was 19% in patients with hyperosmolar non-ketotic coma in Cape Town. The mortality rate was 3% in mild diabetic ketoacidosis (DKA) and 11% in severe DKA in their patients.

Because of the paucity of metabolic data, we have attempted to provide a concise review of the pathophysiology of both type 1 and type 2 diabetes in SSA regions. The limited metabolic data (albeit increasing) from individuals in the SSA can also contribute significantly

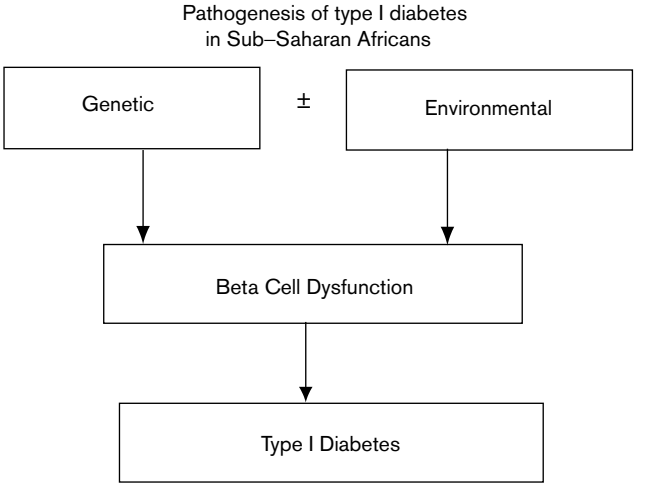
1350-6277 © 2003 Lippincott Williams & Wilkins DOI: 10.1097/01.hjr.0000060841.48106.a3

to the understanding of the effects of migration and genetics on the pathophysiology of type 2 diabetes in the African Diaspora because of the historical link of people of SSA with those in the West Indies, that is, Afro-Caribbeans, Afro-Caribbeans living in Europe (UK and France), Jamaicans, Black Brazilians and African Americans [1–4,15,24].

Type 1 diabetes in Africans in the sub-Saharan region

The hallmark of type 1 diabetes is absolute insulin deficiency due to beta-cell destruction. The disease is characterized by increased propensity for diabetic ketoacidosis or ketosis (Fig. 1). The initial presentation in patients with type 1 diabetes in SSA is either diabetic ketoacidosis or severe hyperglycaemia with minimal ketosis [6,8,11,13,14,17]. This mode of presentation may be determined by the age of the patients, urban versus rural location of the patients and proximity and accessibility to health care providers. Because of limited health care facilities in most SSA countries, and with less expertise in diabetes management in Black Africans, it is presumable that those type 1 diabetic patients in rural areas are less likely to survive the acute diabetic ketoacidosis or severe hyperglycaemic syndrome [12,14,16,17]. In this regard it is estimated that most native Africans with type 1 diabetes, aged less than 15 years, who live in rural areas will die within the first year after diagnosis. These patients perhaps die from the acute metabolic complications of the disease and/or acute infections because of concomitant depressed immunity [11,15–17]. In adults or individuals living in the urban areas and cities in the SSA regions where there are disproportionately greater medical facilities and health care providers as well as easier access to medical care (either private or governmental), the adult type l diabetic patients are more likely to survive the initial severe hyperglycaemia with and without ketosis.

Fig. 1



Pathogenetic mechanism of type 1 diabetes in sub-Saharan Blacks.

The role of autoimmunity in type 1 diabetes in SSA

In the western industrialized world, the autoimmunity in type 1 diabetic patients is commonly reflected as autoinsulin antibodies (AIA), islet cell antibodies (ICA) and glutamic acid decarboxylase enzyme antibodies (GAD). The prevalence of these autoantibodies ranges from 60, 75 and 85% respectively at the time of initial presentation of Caucasians with type 1 diabetes in the western countries. Systematic data on autoimmune markers for type 1 diabetes in native Africans are not available. Autoimmune antibodies to islet cells have been studied in Tanzanian [25] and South African [26,27] patients with type 1 diabetes. McLarty *et al.* [25] found that the prevalence of ICA antibodies was only 8–11% in the newly diagnosed type 1 diabetic patients in Tanzanians. Panz *et al.* [26] found that 44 out 100 blacks (44%) with newly diagnosed, type 1 diabetes had GAD antibody positivity. This would indicate that approximately half of newly diagnosed type 1 diabetic patients in South Africa may have non-autoimmune-mediated type 1 diabetes (type 1B) based on conventional assays. Thus, it can be speculated that the genetic susceptibility and risk factors for type 1 diabetes in SSA regions may be different from those in the western world and that non-autoimmune factors may be the major determinants of type 1 diabetes in SSA. In this regard, it is theoretically possible that diseases such as chronic pancreatitis, infections and chronic exposure to environmental toxins may be the leading aetiopathogenetic candidates for the development of beta-cell failure in susceptible sub-Saharan Africans. Because of the rarity of autoimmunity in adult type 1 diabetic patients and the similarities in the clinical presentation of adults with type 1 diabetes and those with type 2 diabetes in SSA, the diagnosis of adults with type 1 diabetes is often complicated and can initially be misconstrued as type 2 diabetes [12,28].

Genetic markers for type 1 diabetes in Africans in sub-Saharan region

There is overwhelming evidence that type 1 diabetes is an autoimmune process with variable presentation. In the Western world, it is well known that the specific Histocompatibility Leukocyte Antigens (HLA) are associated with type 1 diabetes mellitus in Europeans and Caucasians residing in western industrialized countries. In the Caucasian population, HLA DR3/DR4 confers individual susceptibility to type 1 diabetes. While the exact susceptibility gene(s) underlying type 1 diabetes in SSA is unknown, it is perhaps different from those of the western world. In this regard, there may be several environmental mediators of beta-cell dysfunction (for

example, infection, cassava) that lead to ultimate beta-cell cytotoxicity and failure in patients with type 1 diabetes.

It is well established that the concordance of type 1 diabetes is approximately 50% in identical twins in the western countries [30,31]. These studies indicate that there is a significant role of nongenetic, environmental mediators or modifiers with respect to the development of type 1 diabetes even in the western world. The concordance and the genetic markers that confer increased susceptibility for type 1 diabetes in Blacks in sub-Saharan regions are unknown. Moreover, we are not aware of surrogate metabolic studies in twins concordant or discordant for type 1 diabetes in SSA regions. While there is obviously some genetic component to type 1 diabetes in SSA regions, there are clearly differences in the putative susceptibility genes when compared with patients in the western countries. For example, the prevalence of genetic markers such as HLA DR3/4 is very low in people of sub-Saharan African Ancestry. Thus, there may be other HLA susceptibility genes that protect individuals in the SSA. Orren *et al.* [32] found that HLA Bw9 was more prevalent in black type 1 diabetic patients living in South Africa. In addition, there was no DR3 and B 8 association found in their type 1 diabetic patients. Data on HLABq1 or major class 1 HLA susceptibility genes located on the short arm of chromosome 6 have yielded inconsistent reports in SSA. Omar *et al.* [33] reported that class II antigens(HLA-D, DR loci) showed significant positive association with HLA-DR-4 and DR3/DR4 heterozygosity. Using allele specific (oligonucleotide) probes, it has been shown that type 1 diabetes is positively associated with alleles DQB*0201 [34,35], DQB*0302 [34–36], DRB*0301 and DRB*0401 [36], while a negative association was found with alleles DQB*0501 [35–37].

Clinical manifestation of type 1 diabetes in sub-Saharan Africa

The clinical manifestations of type 1 diabetes in SSA region have been reported to vary considerably [8,9,11–14]. Recent evidence indicates that the prevalence of type 1 diabetes is increasing in Black Africa [1–10]. There are several factors that could account for the rise in type 1 diabetes. First, we have attributed this phenomenon to the increasing awareness and better ascertainment of the diagnosis of diabetes in these populations when compared with previous decades. Secondly, the universal diabetes awareness campaign and advances in medical health care in SSA have improved the patient survival rates in adults with type 1 diabetes and hence the likelihood of affirmation of diagnosis.

The age of onset of type 1 diabetes in SSA is of great interest. While in the western world the majority of patients presenting with type 1 diabetes are children and adolescents, type 1 diabetic patients in the SSA are often older and manifest the disease in the third and fourth decades. Papoz *et al.* [12] examined 310 newly diagnosed cases of diabetes in Ivory Coast and Niger. The prevalence of type 1 diabetes was 11.3% in their population. More than 50% of the patients were over 35 years old. Ducorps *et al.* [21] have also shown that the mean age for a newly diagnosed type 1 diabetic patient is 40.9 years when compared with that for type 2 diabetes of 49.0 years in Black Africans. In a recent survey of 485 diabetic patients attending the University Diabetes Clinic at Accra, Ghana, we identified 60 type 1 diabetic patients. The mean range of age for the onset of the type 1 diabetes was in the mid 30s with a mean age for the patients of 48 years which was only slightly less than the mean age of 51 years in the type 2 diabetic patients in our university clinic [9,10].

Overall glycaemic control in patients with type 1 diabetes remains poor in the SSA region. The blood sugars are often extremely high at the time of presentation, usually over 350 mg/dl with an average glycated haemoglobin exceeding 9.5% in type 1 diabetic patients. Despite the severity of hyperglycaemia, ketosis is uncommon in our adult type 1 diabetic patients [9,10]. When treated with subcutaneous insulin administration, these patients in SSA regions often achieve reasonable glycaemic control which is often associated with weight gain. Because a significant proportion of patients with type 1 diabetes in SSA are lean or non-obese and initially manifest their disease at ages similar to that of type 2 diabetic patients, establishing the diagnosis of type 1 diabetes for epidemiological and resources allocation in these countries is often difficult. Thus, future studies should attempt to include confirmation of the disease subtypes using autoimmune markers (AIA, ICA and GAD) and/or beta-cell functional assessment (such as c-peptide).

Type 2 diabetes in Africans in the sub-Saharan region

Prevalence of type 2 diabetes in the sub-Saharan region

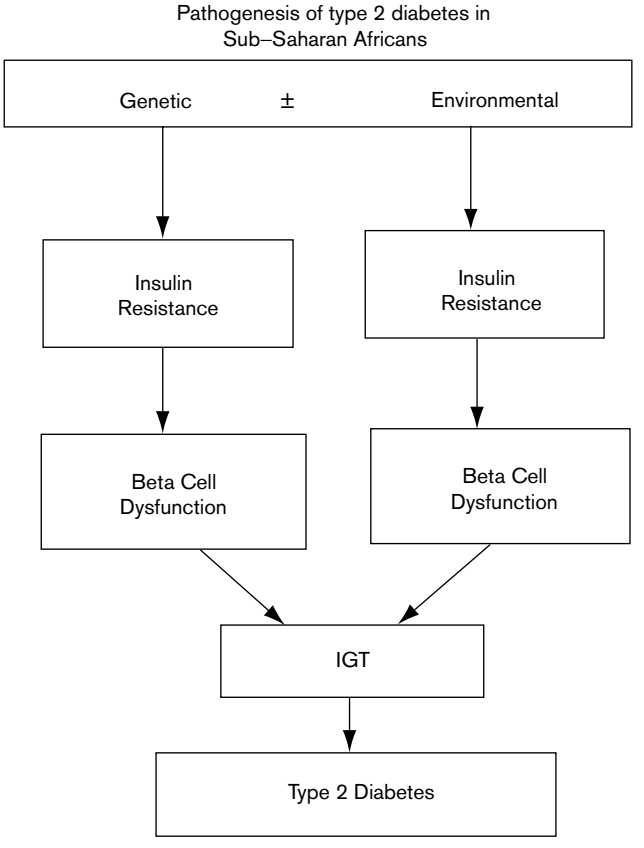
Type 2 diabetes is a genetic disease with strong familial and environmental components [29,30,38,39]. There is an increasing prevalence rate and in some countries epidemic of type 2 diabetes around the world [1–4]. Black Africans living in rural and urban regions of Africa are no exception. In this regard, King *et al.* [1,2] and Seidell *et al.* [3] have provided recent epidemiological data to show the projected global incidence and the prevalence of type 2 diabetes in the world [1–4,39–41]. Ninety percent of the patients are type 2 diabetic patients. The increasing prevalence of type 2 diabetes in SSA regions can be partly ascribed to modernization and adoption of western lifestyle with the associated increased caloric dense diets, less physical activity and

obesity [40]. Thus, there are modifiable risk factors that can be implemented to prevent or slow the rate of type 2 diabetes in these SSA regions [41].

Assessment of beta-cell function in healthy nondiabetic SSA

Type 2 diabetes is characterized by a dual defect of insulin resistance and beta-cell dysfunction (Fig. 2). However, because of the complexity of type 2 diabetes, several approaches have been employed simultaneously to assess beta-cell function and its relationship to insulin action in people with and without glucose intolerance residing in various parts of Black sub-Saharan Africa. These include standard oral glucose tolerance test, homeostasis model assessment (HOMA, %B), intravenous glucose tolerance test (IVGTT), and frequently sampled intravenous glucose tolerance test (FISGT), coupled with the measurement of serum insulin and/or c-peptide. In general, serum insulin and/or c-peptide levels are reported to be lower in non-diabetic Black Africans in South Africa than White South Africans [42–45]. However, data from the Ghanaian population indicated that non-diabetic Ghanaian immigrants to USA had greater serum insulin levels but intact c-peptide levels when compared with White Americans [42]. The findings were similar to those found in the African Americans living in USA [42]. Of great interest, recent and remote migrants of people of West African ancestry to the western world and native Africans manifest peripheral hyperinsulinaemia and insulin resistance but similar serum c-peptide responses when compared with their white counterparts [44]. These studies suggest alterations in insulin clearance and perhaps the decreased hepatic insulin extraction in people of healthy West African ancestry. The mechanism of the defective hepatic insulin clearance in the people of SSA regions remain uncertain.

Fig. 2



Pathogenetic mechanism of type 2 diabetes in sub-Saharan Blacks.

Beta-cell function in prediabetic in SSA

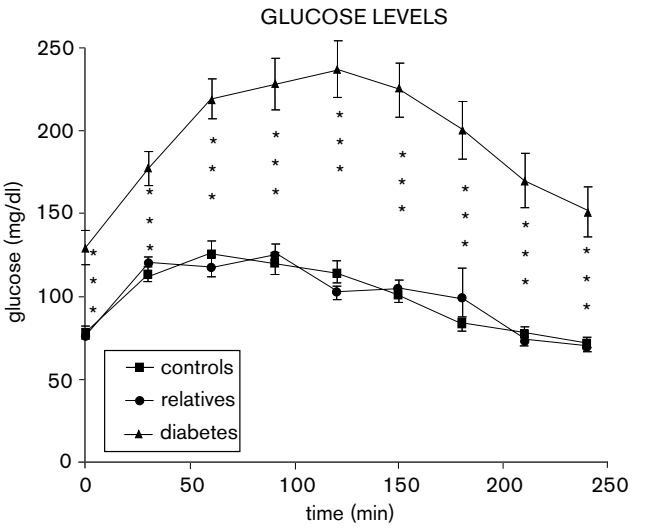
Several genetic and metabolic factors predict impaired glucose tolerance (IGT) and type 2 diabetes in non-African populations. These include first-degree relatives and offspring of patients with type 2 diabetes, former gestational diabetic patients and racial and ethnic groups with increased propensity for IGT and type 2 diabetes. However, the metabolic predictors of IGT and type 2 diabetes are uncertain in non-diabetic subjects of the sub-Saharan region. Several studies in non-African populations have indicated a blunted acute first insulin release after intravenous glucose load or 30 min after oral glucose challenge predict future development of type 2 diabetes. Thus, data on individuals at risk for either IGT or type 2 diabetes such as offspring or first-degree relatives of African patients with type 2 diabetes could provide the necessary risk factor profile in SSA [43,45,46]. Ezenwaka *et al.* [46] found lower acute first phase insulin secretion in non-diabetic, first-degree relatives of patients with type 2 diabetes residing in Ibadan, Nigeria when compared with healthy controls without family history of diabetes. In addition, Mbanya *et al.* [47] have reported that the plasma insulin levels at 30 min after an oral glucose load are lower in first-degree relatives of type 2 diabetic parents who originated from Cameroon when compared with the age- and sex-matched healthy controls without a family history of diabetes. In contrast, we have found that normal glucose-tolerant, first-degree relatives of Ghanaian patients with type 2 diabetes manifest hyperinsulinaemia after both oral and intravenous glucose challenge when compared with the healthy controls [45]. These findings were similar to those of African Americans and Afro-Caribbeans residing in USA and UK respectively. Since these populations have a common genetic heritage and ancestry, we are unable to explain the discrepancies in the serum insulin and/or c-peptide responses to standard oral glucose challenge in the people of SSA. In this regard, the mean body mass indices of the SSA were 22, 22 and 26 kg/m^2 in the Cameroonian, Nigerian and Ghanaian study cohorts respectively. Therefore, we are tempted to conjuncture that differences in body weight and body fat

content and distribution and insulin sensitivity indices as well as differences in physical activity are the putative modulators of insulin responses to various stimuli among populations of African ancestry. We believe longitudinal metabolic studies in diverse SSA populations, similar to the study by Weyer *et al.* [48] conducted in Pima Indians, will be necessary to address the discrepancies in beta-cell function in future.

Beta-cell dysfunction in impaired glucose tolerance and type 2 diabetes in sub-Saharan Africans

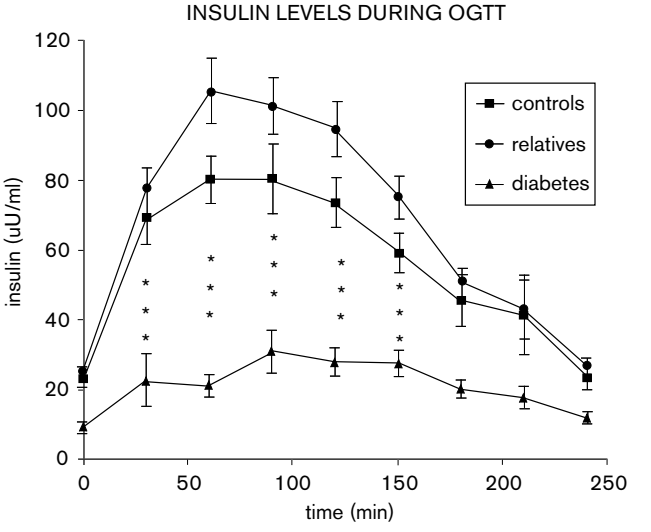
Several studies have examined the beta-cell secretion in sub-Saharan Africans with impaired glucose tolerance and type 2 diabetes [48–55]. Similar to other populations in the western world, SSA patients with IGT and type 2 diabetes manifest blunted acute first insulin secretion to intravenous glucose tolerance test. We have conducted metabolic studies to examine serum insulin/c-peptide responses to glucose in West African patients with IGT and type 2 diabetes (Figs 3–6). During the oral glucose tolerance test (OGTT), serum insulin (Fig. 4) and c-peptide (Fig. 5) responses were significantly lower in the patients with type 2 diabetes. Indeed, the early phase insulin release at 30 min was also blunted in patients from the sub-Saharan regions similar to those found in other populations [49–53]. The patients with IGT had slightly higher total serum insulin and c-peptide responses comparable to those of the non-diabetic subjects. However, this occurred at the expense of the higher postprandial serum glucose levels in the IGT patients with significantly lower insulin : glucose ratios when compared with that of healthy control subjects (Fig. 3). Mbanya *et al.* [47] found a significant proportion of the offspring of Cameroonian patients with type 2 diabetes had either type 2 diabetes (4%) or impaired glucose tolerance test (8.5%). Similarly, the acute first phase insulin responses to intravenous glucose were moderately blunted in the patients with IGT (Fig. 6). We should note that the acute first phase insulin (Fig. 6b) and c-peptide (Fig. 6c) responses to intravenous glucose challenge was also severely blunted in West African patients with type 2 diabetes. Similarly, Shires *et al.* [52] have demonstrated that Black Africans living in South African have lower serum c-peptide when compared with Europeans and Indians. Because most of these studies were cross-sectional, the sequential changes in beta-cell function could not be assessed in the sub-Saharan African patients. The limited longitudinal studies on beta-cell function in patients in SSA suggest rapid deterioration of beta-cell function from IGT to type 2 diabetes in Black versus White South Africans. Joffe *et al.* [50] have demonstrated that the beta-cell function deteriorates more rapidly in the progression of IGT to type 2 diabetes in Black Southern African patients than their white counterparts. In summary, these studies demonstrate that (1) the severity of beta-cell secretory dysfunction varies considerably in SSA populations and (2) moderate to severe beta-cell dysfunction is a paramount pathogenetic feature of both IGT and type 2 diabetes, respectively, in patients in the sub-Saharan region.

Fig. 3



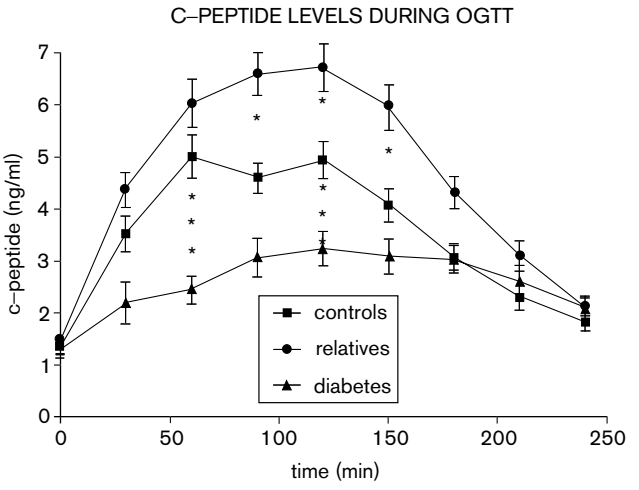
Serum glucose responses to oral glucose tolerance test (OGTT) in native West Africans (Ghanaians) with normal glucose tolerance, and type 2 diabetes. Symbols: closed circles = first-degree relatives of patients with type 2 diabetes. Closed squares: healthy controls without family history of diabetes. Closed triangles: type 2 diabetic patients. To convert mg/dl to mmol/l, divide by 18.

Fig. 4



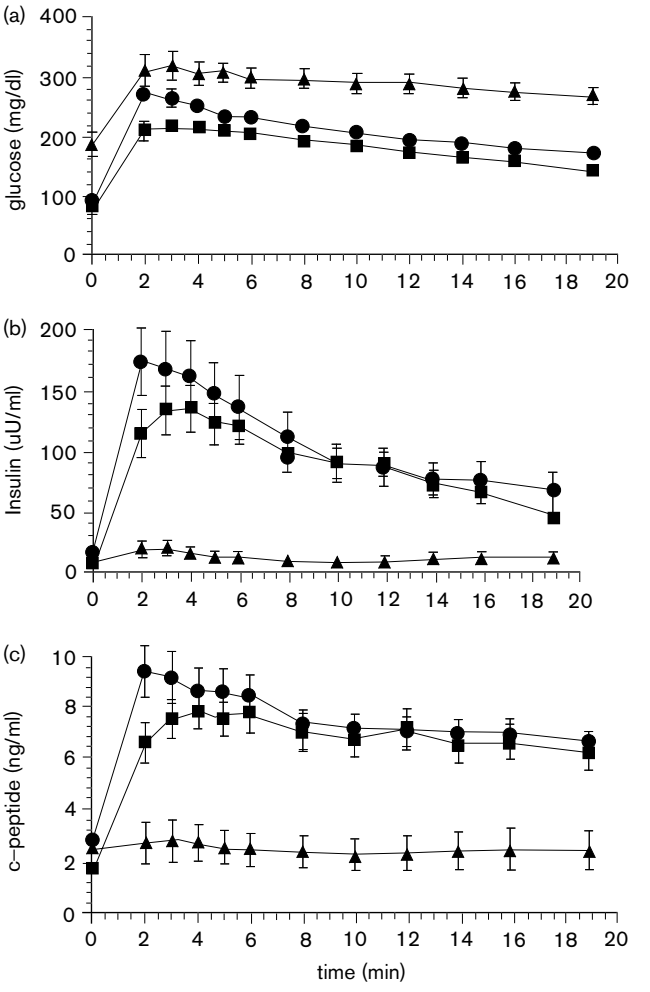
Serum insulin responses to oral glucose tolerance test (OGTT) in native West Africans (Ghanaians) with normal glucose tolerance, and type 2 diabetes. Symbols: closed circles = first-degree relatives of patients with type 2 diabetes. Closed squares = healthy controls without family history of diabetes. Closed triangles = type 2 diabetic patients. To convert uU/ml to pmol/ml, multiply by 6.

Fig. 5



Serum c-peptide responses to oral glucose tolerance test (OGTT) in native West Africans (Ghanaians) with normal glucose tolerance, and type 2 diabetes. Symbols: closed circles = first-degree relatives of patients with type 2 diabetes. Closed squares = healthy controls without family history of diabetes. Closed triangles = type 2 diabetic patients. To convert ng/ml to nmol/ml, multiply by 0.33.

Fig. 6



Serum glucose (a), insulin (b) and c-peptide (c) responses to intravenous glucose tolerance test in native West Africans (Ghanaians) with varying degrees of glucose tolerance. Symbols: closed circles = impaired glucose tolerance. Closed squares = healthy controls without family history of diabetes. Closed triangles = type 2 diabetic patients. To convert mg/dl to mmol/l, divide by 18. To convert uU/ml to pmol/ml, multiply by 6. To convert ng/ml to nmol/ml, multiply by 0.33.

Potential factors affecting beta-cell function in type 2 diabetes in SSA

The reasons for the inconsistencies reported with respect to serum insulin and/or c-peptide responses in diverse sub-Saharan African populations residing in different geographical locations are uncertain. However, several possibilities can be entertained. First, there may be differences in the impact of obesity and body fat distribution and perhaps lifestyle, as well as physical activity and fitness on *in vivo* insulin sensitivity. Hence the variations in serum insulin and c-peptide responses among the various subjects in SSA regions. The latter may be modulated or influenced by the degree of urbanization and westernization in the country [36]. Second, the people of SSA regions are perhaps genetically and phenotypically heterogeneous. Third, several studies have shown that the major determinants of the insulin secretion to stimulation include genetic inheritance and race/ethnicity and the prevailing insulin sensitivity [44,50,52,53]. Most importantly, the prevalent and incident rates of IGT and type 2 diabetes parallel the degree of obesity in various ethnic and racial populations. Fourth, beta-cell secretion is genetically determined in several populations. In the White populations residing in Europe, Vaag *et al.* [38] have reported significant interindividual, insulin secretion in their identical twins discordant for type 2 diabetes in Finland. Fifth, beta-cell secretion is found to be much lower in Black South Africans when compared with Whites. Previous investigators have demonstrated that West Africans (Ghanaians) with mild fasting hyperglycaemia and type 2 diabetes manifest disproportionately lower beta-cell function during fasting and oral glucose and intravenous glucose challenge in sub-Saharan Africans [49,51]. Shires *et al.* [52] reported decreased beta-cell maximal capacity in obese Black South Africans when compared with their White counterparts. Thus, we speculate that SSA subjects could be genetically predisposed to accelerated apoptosis with rapid deterioration of beta-cell, especially in the face of metabolic stressors. Sixth, the beta-cell dysfunction in Black sub-Saharan Africans could be initiated in intrauterine (in utero) fetal life during pregnancy. These fetuses could experience generalized, growth retardation, that is, 'small for gestational age babies' and hence impaired beta-cell functional integrity, due to poor maternal nutrition. Similarly, it is possible

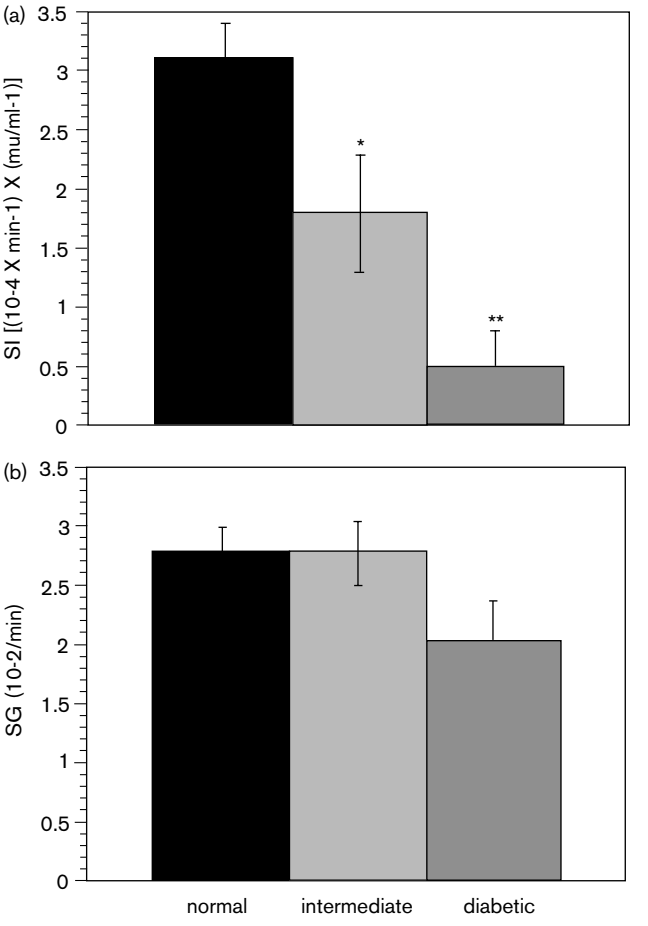
that early childhood malnutrition (for example, kwashiorkor – protein deficient, or marasmus – total energy deficient malnutrition) results in beta-cell dysfunction during adulthood. In this regard, Crowther *et al.* [56] have demonstrated that children with low birth weight had rapid post-natal weight gain, higher plasma insulin at 30 and 90 min and higher serum glucose responses at 30 min at the age of 7 years during OGTT when compared with normal weight babies.

Several potential environmental beta-cell cytotoxic agents could play a role in the etiology of type 2 diabetes in SSA regions. In this regard, cassava has been implicated. However, recent studies have questioned the validity of the causal effect of cassava in beta-cell dysfunction in SSA due to methodological problems in these studies. Nevertheless, it is possible that environmental toxins, in combination with a defective nutritional environment and chronic exposure to environmental toxins such as cassava, alcohol or childhood bacterial, viral and parasitic infections, such as malaria or antimalarial agents, could play a role. The inflammatory origin of type 2 diabetes as assessed by markers such as interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α) and c-reactive proteins(CRP) will be of great interest in SSA regions.

The role of insulin resistance in the pathogenesis of type 2 diabetes in SSA

Insulin resistance is the hallmark of type 2 diabetes in the western world [3,31,47,54–57]. The insulin resistance is genetic and familial with acquired component [37,56,68]. It is found predominantly in the skeletal muscle and hepatic tissues in several populations. It precedes the development of IGT and type 2 diabetes by decades. Indeed, insulin resistance is found in non-diabetic hypertensive subjects, non-diabetic, obese subjects and non-diabetic subjects with parents with type 2 diabetes. It is now clear that race and ethnicity, independent of family history of type 2 diabetes, also determine insulin resistance in several populations [43,45,58]. Recent studies have demonstrated that insulin resistance tracks with obesity in a given population. The consequences of the insulin resistance are progressive deterioration in the rate of glucose disappearance or disposal in the peripheral tissues and perhaps *beta-cell exhaustion.* The latter, whether or not it is genetically inherited (e.g. apoptosis), could precipitate the development of IGT and type 2 diabetes in individuals susceptible to the disease. As shown in Figure 7 (upper panel), we have demonstrated a reduced insulin sensitivity index (SI) in newly diagnosed, immigrant Ghanaian patients with both IGT and type 2 who were residing in USA. We have recently confirmed these findings in indigenous Ghanaian patients with IGT and type 2 diabetes who reside in the native country [48]. The reduced insulin sensitivity index was also found in

Fig. 7



Insulin sensitivity index (SI) (a) and glucose effectiveness (SG) (b) in native West Africans (Ghanaians).

the non-diabetic first-degree relatives of our native Ghanaian patients with type 2 diabetes [49]. This was consistent with the earlier findings by Ezenwaka *et al.* in first-degree relatives of Nigerian patients with type 2 diabetes [46]. Thus, insulin resistance is a concomitant feature of type 2 diabetes in people of the sub-Saharan region and appears to antecede the development of clinical disease by decades.

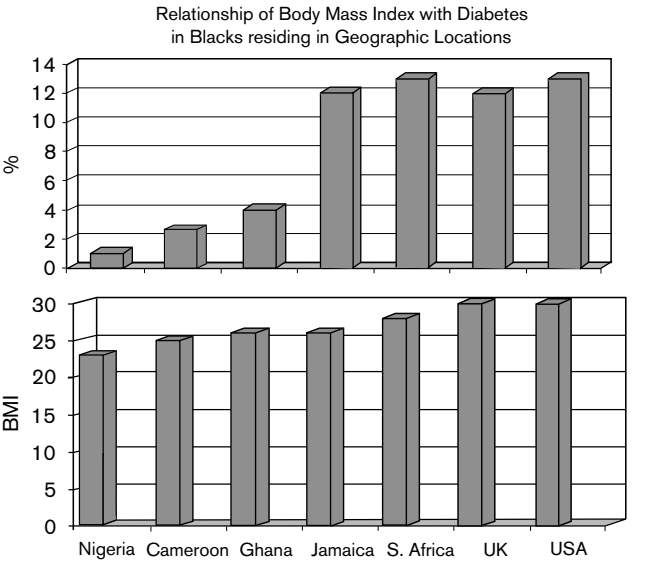
Obesity and insulin action in SSA regions

In western industrialized countries, the major determinants of insulin resistance, in addition to genetics, are obesity [body mass index (BMI) $> 30\,kg/m^2$] or overweightness (BMI $> 25\,kg/m^{2)}$ for females and for males) and sedentary lifestyle. Thus, in populations with lower prevalence of obesity such as native Black Africans, it has been suggested that the degree of insulin resistance is predominantly determined by the genetic inheritance which is aggravated by acquisition of conventional risk factors such as obesity or physical inactivity. However, the

emerging evidence indicates that, in developing countries, there is a strong association of obesity with IGT and type 2 diabetes even with only moderate weight gain and BMI between 25–30 kg/m^2 [8,11,24]. As can be seen in Figure 8, slight increases in BMI from 22 to 25 kg/m^2 was associated with almost doubling of the prevalence of type 2 diabetes in the diverse populations of SSA origin residing in different geographic locations and with varying rates of obesity.

The prevalence of obesity in Blacks residing in SSA has been estimated at 10–15% [6]. This is remarkably lower than the prevalent rate of 50% in African Americans and 35% in Afro-Caribbeans residing in the USA and UK respectively. Similar to other populations, the prevalence of obesity in patients with IGT and type 2 diabetes residing in the sub-Saharan areas ranges between 40–60% [6,8,11]. However, a remarkable number of patients with IGT and type 2 diabetes in sub-Saharan African are lean or maintain normal body weight. This is in great contrast with the 90% prevalence of obesity (BMI of 30 kg/m^2) found in African Americans and Afro-Caribbeans residing in the UK. As shown in Figure 8, several investigators have found a positive and direct relation between the prevalence of obesity and type 2 diabetes in patients living in Ibadan in Nigeria [24], Dar es Salem in Tanzania [8] and in Cape Town, South Africa [20].

Fig. 8



Relationship of body mass index (BMI) and prevalence (%) of type 2 diabetes in selected Black populations residing in different geographic regions.

Another risk factor for the development of type 2 diabetes is upper body obesity. The distribution of body fat has been associated with insulin resistance and the metabolic syndrome [3,57,58]. In this regard, assessment of body fat distribution could also be very important in individuals residing in the sub-Saharan regions. In western, industrialized countries, increased intra-abdominal fat content or visceral adiposity is regarded as a risk factor for both type 2 diabetes, hypertension, hypertriglyceridaemia and cardiovascular diseases, hence the insulin resistance or metabolic syndrome. The increased visceral adiposity is purported to be associated with increased flux of free fatty acid (FFA) to the liver with enhancement of gluoneogenesis and increased hepatic glucose production and hepatic triglyceride synthesis. This concept has not been proven in native Africans residing in the sub-Saharan regions and indeed remains controversial in other Black populations such as African Americans. Recently, Van der Merwe *et al.* [59] measured the intra-abdominal adiposity (VA) using computerized tomographic scan (CAT) of the abdomen in women with type 2 diabetes residing in South Africa with various ethnic populations. The diabetic Black women had increased visceral adiposity associated with higher serum leptin and FFA levels but paradoxically lower serum insulin levels when compared with diabetic White women in South African. It is important to note that adult African American women and children residing in the USA have lower intra-abdominal visceral adiposity but, paradoxically, increased plasma insulin and insulin resistance when compared with White counterparts with similar BMI. Because of these discrepancies, it is worthy to note that the prevalent rates of the individual components of the insulin resistance or dysmetabolic syndrome may vary in diverse sub-Saharan regions with variable ethnic groups. The lack of availability of sophisticated, high resolution CAT scan to assess visceral and regional body fat distribution limits further studies in this area in SSA regions. However, we believe simple non-invasive, less expensive, methods such as measurement of waist circumference and waist–hip circumference ratio to assess the body fat distribution pattern, and the use of a bioelectrical impedance analyzer (BIA) and dual energy X-ray absorb (DEXA) will be sufficient.

In summary, the molecular mechanism(s) of insulin resistance in Blacks of sub-Saharan regions remains unknown. In non-African populations, the insulin resistance manifests as reduced glycogen storage and is regarded as a post-receptor defect in the activation of glycogen synthase. Whether abnormalities in the insulin receptor number and affinity as well as insulin receptor substrate-1 and -2 (IRS–1 and 2), intermediate metabolic pathways, glucose transporters, etc. exist in sub-Saharan Africans with insulin resistance, glucose intolerance and type 2 diabetes remain to be investigated. We are convinced that the ongoing study of people of sub-

Saharan African origin for susceptibility genes for type 2 diabetes could provide the genetic basis for the disease in people of African diaspora [45].

The role of glucose-mediated glucose disposal in Africans residing in the sub-Saharan region

A major component of maintaining glucose tolerance in humans is the ability of glucose to mediate its own transport and suppress basal hepatic glucose production [42,43,49,51,56,60–65]. This mechanism has been termed non-insulin-mediated glucose disposal or glucose effectiveness (SG). Bergman RN [60] and Best *et al.* [65] have demonstrated that alterations in SG play a significant role in the development of IGT and type 2 diabetes in several populations. Alterations in this non-insulin-mediated, facilitated, glucose disposal, SG, has been implicated in the hyperglycaemia found in several nonSSA populations with glucose intolerance and type 2 diabetes. In this regard, SG is reported to be reduced in Caucasian [52] and Japanese [61,62] patients with IGT and type 2 diabetes when compared with their non-diabetic counterparts. In the White offspring of patients with type 2 diabetes, Martin *et al.* [57] reported that a reduced SG in the face of insulin resistance appears to be a major predictor of future type 2 diabetes in Caucasians.

We have conducted extensive studies in SG in both adult and adolescent Blacks residing in diverse geographic countries with and/or without IGT and type 2 diabetes using frequently sampled intravenous glucose tolerance tests and the minimal model method in people of SSA ancestry [42,43,49,51]. As shown in Figure 7b, we have demonstrated that at the time of IGT, the SG is reduced by approximately 30% in African Americans [53], Ghanaian immigrants to USA [51] and Ghanaians residing in their native countries when compared with their healthy, non-diabetic subject counterparts in our cross-sectional studies. Most importantly, we also demonstrated that the lower SG found in IGT in African Americans and Ghanaians does not further deteriorate during the development of type 2 diabetes [49,51,53]. Of great interest is that the SG in Ghanaians, irrespective of their country of residency, was comparable to those of African Americans (remote immigrants). Note that SG is normal in insulin-resistant offspring of patients with type 2 diabetes residing in SSA regions [45,49]. Thus, we are tempted to speculate that SG appears to be well preserved and conserved for generations in remote immigrants and indigenous people of SSA region. We believe that the conserved SG could have teleological implications in promoting preferential glucose transport beyond that of insulin-mediated glucose disposal. We have postulated that the preservation of SG appears to be a major component of the *putative thrifty gene* in the West African diaspora [66,67]. This interesting hypothesis deserves to be investigated in people of SSA regions with or without IGT and type 2 diabetes. Whether a reduced SG is a predictor of future development of IGT and type 2 diabetes in native Africans at risk for type 2 diabetes remains to be investigated in longitudinal and prospective studies in native sub-Saharan Africans.

Potential role of environmental factors in the pathogenesis of type 1 diabetes and type 2 diabetes in Africans residing in the sub-Saharan region

Geographical location

Papoz *et al.* [12] and others have indicated that there are differences in the clinical presentation of type 2 diabetes in SSA. The thin type 2 diabetic patients are often from rural areas and the clinical picture is similar to that of type 1 diabetic patients. The BMI of the non-obese type 2 diabetic patients was approximately 22 kg/m^2 similar to that of their type 1 diabetic patients. In addition, the beta-cell function in the non-obese type 2 diabetes patients is severely diminished at fasting and during glucose challenge. As expected, the serum c-peptide values were significantly lower in the lean than in the obese type 2 diabetic patients. In addition, the obese type 2 diabetic patients often reside in cities or urban areas. Thus, westernization with its associated obesity and insulin resistance tends to modify the metabolic characterization of type 2 diabetes in SSA.

Subtypes of diabetes in Africa

Undoubtedly, diabetes has a multivariate expression and presentation in SSA. Thus, there are subtypes of diabetes in SSA and developing countries such as SSA, subcontinental India and Jamaica. Typically, the lean type 2 diabetic patients in SSA regions could be described as insulin-sensitive or insulin-resistant variants in these populations. Therefore, there is often confusion between type 1 diabetic and non-obese type 2 diabetic patients with the malnutrition-related diabetes mellitus (MRDM) at the time of initial presentation. The latter occurs as fibrocalcific pancreatitis with associated type 2 diabetes in patients less than 30 years old. These patients are extremely thin with BMI $< 19\,kg/m^2$, blood sugars in excess of 18 mmo1/1 (350 mg/dl), have no ketonuria despite elevated glucagon and manifest high insulin requirements greater than 2 U/kg per day. Characteristically, these patients have a past history of severe malnutrition in childhood and radiological evidence of calcific pancreases.

Impact of culture and ethnicity in the pathogenesis of type 1 and 2 diabetes is SSA

Several factors could confound the pathophysiology and the ultimate development and manifestations of type 1 and type 2 diabetes in patients residing in SSA regions. First, there is habitual use of uncontrolled and unregu-

lated medications without physician supervision (for example, diuretics, glucocorticoids). Second, there is a common practice of using traditional herbal medications with unproven efficacy for type 2 diabetes and other diseases in most SSA regions. This could have serious consequences on the presentation and acute complications of both type 1 and type 2 diabetic patients. Third, because of the epidemic of HIV positivity and AIDS in some sub-Saharan Africa countries, the use of antiretroviral protease inhibitors will continue to increase [68]. In conjunction with possible direct viral beta-cell toxicity, the use of antiviral protease inhibitors, with the associated insulin resistance(that is, Crixivan syndrome), it is conceivable that the rate of type 2 diabetes in the AIDS patients who survive the disease could increase. Another confounding variable is the use of pentamidine as prophylaxis for *Pneumocystis carinii* pneumonia in AIDS and HIV-positive patients. Pentamidine has severe beta-cell cytotoxic effects which could be implicated in the development of either type 1 or type 2 diabetes in the AIDS patient in sub-Saharan Africans. Fourth, people of sub-Saharan regions are chronically exposed to cyanide in cassava roots, a major staple in the diets of most people in the sub-Saharan regions. This has been implicated in the pathogenesis of malnutrition-related and fibrocalcific pancreatic type 2 diabetes, but this remains debatable [69]. Fifth, in most of sub-Saharan countries, the commonest but socially acceptable 'beta-cell toxin' is alcohol, which has the potential of destroying the beta-cells with subsequent development of IGT and type 2 diabetes. Finally, intrauterine fetal growth retardation and/or early childhood malnutrition with consequent reduction in pancreatic islet cell mass and functional integrity could have potential effects on the development of type 1 and type 2 diabetes in adult Africans [56,70,71]. Indeed, recent studies by Young *et al.* [69] and by Omar *et al.* [70] in people of sub-Saharan ancestry found excess maternal factors in the transmission of type 2 diabetes than the paternal history of type 2 diabetes.

Summary and conclusions

In summary, the prevalent and incident rates of type 1 and type 2 diabetes are increasing in the sub-Saharan regions of African with a persistent rural to urban gradient when compared with decades ago. We believe the increase in prevalence of diabetes in SSA can be ascribed partly to better disease ascertainment and adoption of western lifestyle. In patients with type 2 diabetes, the pathogenetic hallmark of the disease is severe beta-cell dysfunction with variable degrees of insulin resistance in SSA populations. The insulin resistance appears to track with obesity, although it may precede and antedate the development of glucose intolerance by decades. With respect to type 1 diabetes in patients residing in SSA, severe beta-cell dysfunction with absolute insulinopaenia, and not insulin resistance, is the paramount prerequisite for the pathogenesis of the disease. However, the low rates of HLA association and the autoimmune antibody raise doubts on the importance of autoimmunity and genetic heritability in the pathogenesis of type 1 diabetes in SSA regions. Finally, the clinical manifestations of both diseases are myriad and overlap considerably, thus requiring a strong index of suspicion and appropriate testing. These variable clinical manifestations are modulated by cultural beliefs and attitudes about the disease as well as the availability and access to health care services. Nevertheless, with the increasing collaboration among researchers in sub-Saharan African regions on one hand and those from advanced and well-sophisticated, established research institutions in the western, industrialized countries on the other, we believe the genetic, metabolic, immunological and environmental components of both type 1 and type 2 diabetic patients residing in the sub-Saharan regions of African could be further elucidated. Understanding of these aetiopathogenetic factors for both diseases could enhance the development of effective preventive strategies and/or management paradigms for patients with type 1 and type 2 diabetes residing in sub-Saharan regions of Africa.

Acknowledgements

We wish to thank the staff of the clinical research center at The Ohio State University Medical Center, Columbus, Ohio USA the technicians at GCRC, Columbus, Ohio USA and Diabetes and Endocrine Research Laboratory of University of Ghana Medical School, Accra, Ghana. The work was in part supported by GCRC– RR 0034.

References

1 King H, Rewers M. Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diab Care* 1993; **16**:157–177.
2 King H, Aubert R, Herman WH. Global burden of diabetes, 1195–1925. Prevalence, numerical estimates and projections. *Diab Care* 1998; **21**:1414–1433.
3 Seidell JC. Obesity, Insulin resistance and diabetes – a world wide epidemic. *Br J Nutr* 2000; **83**:S5–S8.
4 Harris ML, Hadden WC, Knowler WC, Bennett PH. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in US population aged 20–74. *Diabetes* 1987; **36**:523–524.
5 Swai AB, McLarty DG, Alberti KG. IDDM in sub-Saharan Africa. *Diab Med* 1993; **10**:188 (commentary).
6 Amoah AGB. Undiagnosed diabetes and impaired glucose regulation in adult Ghanaians using the ADA and WHO diagnostic criteria. *Diabetologia* 2002; **39**:7–13.
7 Sidibe el-H. Diabetes mellitus in sub-Saharan Africa. *Sante* 1998; **8**: 342–346.
8 McLarty DG, Pollitt C, Swai AB. Diabetes in Africa. *Diab Med* 1990; **7**: 670–684.
9 Kalk WJ, Huddle KR, Rall FJ. The age of onset and sex distribution of insulin dependent diabetes in Africans in South Africa. *Postgrad Med J* 1993; **69**:553–556.
10 Gill GV, Huddle KR. Patterns of insulin dependence in an African diabetic clinic. *QJM* 1991; **81**:829–835.
11 Swai AB, Lutale J, McLarty DG. Diabetes in tropical Africa: a prospective study, 1981–1987. I. Characterization of newly presenting patients in Dar es Saleem Tanzania, 1981–1987. *BMJ* 1990; **300**:1103–1106.
12 Papoz L, Delcourt C, Potom-Sanchez A, Darrack R, Toure IA, Cuisinier-Rayal JC. Clinical classification of diabetes in tropical West African. *Diab Res Clin Pract* 1998; **39**:219–227.

13 Levitt NS, Bradshaw D, Zwarenstein MF, Bawa AA, Maphumoto S. Audit of public sector primary diabetes care in Cape Town, South Africa. High prevalence of complications uncontrolled, hyperglycemia and hypertension. *Diab Med* 1997; **14**:1073–1077.
14 Chale SS, Swai AB, Mujinja PG, McLarty DG. Must diabetes be fatal in Africa? Study of cost of treatment. *BMJ* 1992; **304**:1215–1218.
15 Wilks R, Rotimi C, Bennett F, McFarlane-Anderson N, Kaufman JS, Anderson SG, Cooper RS, *et al.* Diabetes in Caribbean: results of a population survey from Spanish Town, Jamaica. *Diab Med* 1999; **16**: 875–883.
16 Alberti KGMM. Insulin dependent diabetes mellitus: a lethal disease in the developing world. *BMJ* 1999; **309**:754–755.
17 Levetan BN, Levitt NS, Bonnici F. Hyperglycemic emergencies are common problem. *S Afr Med J* 1997; **87**:368–370.
18 Mabanya JC, Ngogang J, Salah IN, Minkoulou E, Balkau B. Prevalence of NIDDM and impaired glucose tolerance in a rural and an urban population in Cameroon. *Diabetologia* 1997; **40**:824–829.
19 Owoeaje EE, Rotimi CN, Kaufinan JS, Tracy J, Cooper RS. Prevalence of adult diabetes in Abadan, Nigeria, *East Afr Med J* 1997; **74**:299–302.
20 Charlton KE, Levitt NS, Lombard CJ. The prevalence of diabetes mellitus and associated risk factors in elderly coloured South Africans. *S Afr Med J* 1997; **87**:364–367.
21 Ducorps M, Ndong W, Jupkwo B, Belmmejdoud G, Poirier JM, Mayaudon H, Bauduceau B. Epidemiological aspects of diabetes in Cameroon: what is the role of tropical diabetes? *Diab Metab* 1997; **23**:761–767.
22 Kalk WJ, Joannou J, Ntsepo S, Mohamed P, Becker PJ. Ethnic differences in the clinical and laboratory associations with retinopathy in adult onset diabetes: studies in patients of African, European and Indians origin. *J Intern Med* 1997; **241**:31–37.
23 Levitt NS, Unwin N, Brashaw D, Kitange HM, Mbanya JC, Molletze WF, *et al.* Application of the new ADA criteria for the diagnosis of diabetes in sub-Saharan Africa. American Diabetes Association. *Diab Med* 2000; **17**: 381–385.
24 Rotimi CN, Cooper RS, Okosun IS, Olatunbosum ST, Bella AF, Wilks R, *et al.* Prevalence of diabetes and impaired glucose tolerance in Nigerians, Jamaicans and US blacks. *Ethn Dis* 1999; **7**:190–200.
25 McLarty DG, Athaide I, Bottazzo GF, Swai AM, Albert KG. Islet cell antibodies are not specifically associated with insulin dependence diabetes in Tanzanian Africans. *Diab Res Clin Pract* 1991; **9**:219–224.
26 Panz VR, Kalk WJ, Zouvanis M, Joffe BI. Distribution of autoantibodies to glutamic acid decarboxylase across the spectrum of diabetes mellitus seen in South Africa. *Diab Med* 2000; **17**:524–527.
27 Omar MA, Botazzo GF, Asmal AC. Islet cell antibodies and other autoantobodies in South African blacks and Indians with insulin dependent diabetes mellitus(IDDM). *Hormone and Metab Res* 1986; **18**:126–128.
28 Erasmus RT, Blanco E, Okesina AB, Gqweta Z, Matsha T. Assessment of glycemic control in stable type 2 black south African diabetics attending a peri-urban clinic. *Postgrad Med J* 1999; **75**:603–606.
29 Joffe BI, Wing JR, Zouvanis M, Pieterse A, Seftel HC. NIDDM in African Americans and black South Africans; many similarities but some important differences. *Diab Care* 1997; **19**:1451–1152.
30 Tattersal RB, Fajans S. Prevalence of diabetes and glucose intolerance in 199 offspring of conjugal parents. *Diabetes* 1975; **24**:452–462.
31 Barrett AK, Eff C, Leslie RDG, Pyke DA. Diabetes in identical twins. A study of 200 pairs. *Diabetologia* 1981; **20**:87–93.
32 Orren A, Taljard D, De Tolt E. HLA-A,B,C and DR antigen association in insulin dependent diabetes mellitus (IDDM) in South African Negro and Cape coloured people. *Tissue Antigens* 1988; **26**:332–339.
33 Omar MAK, Hammond MG, Asmal AC. HLA-A,B,C and DR antigens in young South African blacks with type 1(insulin-dependent) diabetes mellitus. *Diabetologia* 1984; **26**:20–23.
34 Magzoub MM, Stephens HA, Gale EA, Bottazzo GF. Analysis of HLA–DR and DQ gene polymorphisms in Sudanese patients with type 1 (insulin-dependent) diabetes. *Immunogenetics* 1991; **34**:366–371.
35 Chuaffert M, Cisse A, Chevenne D, Parfait B, Michel S. Trivin HLA-DQ beta 1 typing and non-ASP 57 alleles in the aborigine population of Senegal. *Diab Care* 1995; **18**:677–680.
36 Garcia-Panccheo JM, Herbut B, Culbush S, Hitman GA, Zhonglin W, Magzoub M, *et al.* Distribution of HLA-DQA1,-DQB1 and DRB1 alleles in black IDDM controls from Zimbabwe. *Tissue Antigens* 1992; **40**:145–149.
37 Otrtenforth TH, Mengistu M, Tadesse G, De Vries RR, Converse PJ. HLA-DR and DQ antigens in insulin-dependent diabetics in Ethiopia. *Tissue Antigens* 1987; **30**:193–197.
38 Vaag A, Henrikson JE, Madsbad S, Holm N, Beck-Nielson H. Insulin secretion, insulin action, and hepatic glucose production in identical twins discordant for non-insulin dependent mellitus. *J Clin Invest* 1995; **95**:690–698.
39 Newman B, Selby JU, King MC, Slemenda C, Fabsite R, Friedman CD. Concordance for type 2 (non-insulin-dependant) diabetes mellitus in male twins. *Diabetologia* 1997; **30**: 763–768.
40 Osterbe T, Welby TJ, Prior IAM, Salmond CE, Stokes YM. Type 2 (noninsulin-dependent diabetes mellitus, migration and westernization; the Tokelau Island Study. *Diabetologia* 1992; **32**:585–590.
41 Levitt NS, Steyn K, Lambert EV, Reagon G, Lombard CJ, Fourie JM, *et al.* Modifiable risk factors for type 2 diabetes in the peri-urban community in South Africa. *Diab Med* 1999; **16**:946–950.
42 Osei K, Schuster DP. Metabolic characteristics of African descendants: a comparative study of African-Americans and Ghanaian immigrants using minimal model analyjsis. *Diabetologia* 1995; **38**: 1103–1109.
43 Osei K, Schuster DP. Ethnic differences in secretion, sensitivity and hepatic extraction of insulin in black and white Americans. *Diab Med* 1994; **11**:755–762.
44 Cruickshank JK, Cooper J, Burnett M, MacDuff J, Drubra U. Ethnic differences in fasting plasma c-peptide and insulin in relation to glucose tolerance and blood pressure. *Lancet* 1991; **11**:338–342.
45 Amoah ABG, Owusu SK, Ayittey OM, Schuster DP, Osei K. Minimal model analyses of beta cell secretion, insulin sensitivity and glucose effectiveness in glucose tolerant, first degree relatives of Ghanaian patients with type 2 diabetes and healthy control subjects. *Ethn Dis* 2001; **11**:201–210.
46 Ezenwaka CE, Akanji AO, Osei K, Adejuwon CA, ODorisio TM, Cottrell DA, Akindale KS. Glucose and serum insulin responses to intravenous glucose challenge in relatives of Nigerian patients with noninsulin-dependent diabetes mellitus. *Diab Res Clin Pract* 1993; **20**:175–181.
47 Mbanya JC, Pam N, Mbanaya DN, Sobngwi E, Ngogang J. Reduced insulin secretion offspring of African type 2 diabetic parents. *Diab Care* 2000; **23**:1761–1765.
48 Weyer C, Tataranni PA, Bogardus C, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance – , – /during each stage of type 2 diabetes development. *Diab Care* 2000; **24**:89–94.
49 Amoah AGB, Owusu SK, Schuster DP, Osei K. Pathogenetic mechanism of type 2 diabetes in Ghanaians-importance of beta cell secretion, insulin sensitivity and glucose effectiveness. *S Afr Med J* 2002; **92**:377–384.
50 Joffe BI, Panz VR, Wing JR, Raal FT, Seftel HC. Pathogenesis of non-insulin dependent diabetes mellitus in the black population of Southern Africa. *Lancet* 1992; **340**:460–462.
51 Osei K, Schuster DP. Decreased insulin-mediated but not non-insulin dependent glucose disposal in glucose intolerance and type 2 diabetes in African (Ghanaian) immigrants. *Am J Med Sci* 1996; **311**:113–121.
52 Shires R, Joffe BI, Seftel HC. Maximal pancreatic beta-cell stimulation and the counterregulatory hormonal responses in South African black and white obese subjects. *S Afr J Med* 1985; **67**:845–847.
53 Osei K, Gaillard T, Schuster DP. Pathogenetic mechanism of impaired glucose tolerance and type II diabetes in African Americans. The significance of insulin secretion, insulin sensitivity and glucose effectiveness. *Diab Care* 1997; **20**:396–404.
54 DeFronzo RA, Ferrannini E, Simonson DC. Fasting hyperglycemia in non-insulin-dependent diabetes mellitus: contributions of excessive hepatic glucose production and impaired tissue glucose uptake. *Metabolism* 1989; **38**:387–395.
55 Reaven GM, Hollenbeck CB, Chen Y-D. Relationship between glucose tolerance, insulin secretion, and insulin action no obese individuals with varying degrees of glucose tolerance. *Diabetologia* 1989; **32**:52–55.
56 Crowther NJ, Cameron N, Trusler J, Gray IP. Association between poor glucose tolerance and rapid post natal weight gain in seven year old children. *Diabetologia* 1998; **41**:1163–1167.
57 Martin BC, Warram JH, Krowleski AS, Bergman RW, Soeldner JS, Kahn CR. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a follow–up study. *Lancet* 1993; **340**:925–929.
58 Osei K, Schuser DP, Owusus SK, Amoah AGB. Race and ethnicity determine serum insulin and c-peptide concentrations and hepatic insulin extraction and insulin clearance: comparative studies of three populations of West African Ancestry and White Americans. *Metabolism* 1997; **46**: 53–58.
59 der Merwe MT, Panz VR, Crowther NJ, Schlapohoff GP, Gray EP, Froguel P, *et al.* Free fatty acids and insulin levels–relationship to leptin levels and body composition in various groups from South Africa. *Int J Obesity Rel Metab Disord* 1999; **23**:909–917.
60 Bergman RN. Toward physiological understanding of glucose tolerance: minimal model approach. *Diabetes* 1989; **38**:1512–1527.

61 Taniguchi A, Nakai Y, Fukushima M, Imura H, Kawamura H, Nagato H, *et al.* Insulin sensitivity and insulin secretion in subjects with impaired glucose tolerance: A minimal model analysis. *Metabolism* 1994; **43**:714–718.
62 Taniguchi A, Nakai Y, Fukushima M, Imura H, Kawamura H, Nagato H, *et al.* Pathogenic factors responsible for future glucose tolerance in patients with NIDDM. *Diabetes* 1992; **41**:1540–1546.
63 Kautzky-Miller A, Pacini G, Ludvik B, Schernthaner G, Prager R. Beta-cell hypersecretion and not reduced hepatic insulin extraction is the main cause of hyperinsulinemia in obese, nondiabetic subjects. *Metabolism* 1992; **41**:1304–1312.
64 Kahn SE, Prager RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, *et al.* The contribution of insulin-dependent and insulin-independent glucose uptake to intravenous glucose tolerance in healthy human subjects. *Diabetes* 1994; **43**:587–592.
65 Best JD, Kahn SE, Ader M, Wantanabe RM, Ta-Ghen N, Bergman RN. Role of glucose effectiveness in the determination of glucose tolerance. *Diab Care* 1996; **19**:1018–1030.
66 Joffe B, Zimmet P. The thrifty genotype in type 2 diabetes: an unfinished symphony moving to its finale. *Endocrine* 1998; **9**:139–141.
67 Osei K. Metabolic consequences of the West African Diaspora: lessons form the thrifty gene. *J Lab Clin Med* 1999; **133**:98–111.
68 Panz VR, Joffe BL. Impact of HIV infection and AIDS on prevalence of type 2 diabetes in South Africa in 2010. *BMJ* 1999;**318**:1351 (commentary).
69 Swai AB, McLarty DG, Mtinnangi BL, Tatala S, Kitnage HM, Mlingi N, *et al.* Diabetes is not caused by cassava toxicity – study in a Tanzanian community. *Diab Care* 1994; **15**:1378–1385.
70 Young CA, Kumar S, Young MJ, Boulton AJ. Excess maternal history of diabetes in Caucasian and Afro-origin non-insulin-dependent diabetic patients suggests maternal factors in disease transmission. *Diab Res Clin Pract* 1995; **28**:47–49.
71 Omar MA, Motala AA, Seedat MA, Pirie F. The significance of a positive family history in South African Indians with non-insulin-dependent diabetes (NIDDM). *Diab Res Clin Pract* 1996; **34**:S13–S16.