

The epidemiology and pathogenesis of type 1 diabetes mellitus in Africa

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Abstract

Type 1 diabetes is a serious, debilitating disease, with life-threatening complications, and the financial burden associated with the management of this disease is enormous. Early diagnosis and intervention can improve morbidity and mortality. Unfortunately, in Africa, type 1 diabetes is poorly characterised, and there is sparse information regarding the aetiology and epidemiology of this disease. However, there is some evidence of a later age of onset in African type 1 diabetic patients, compared to European diabetics, and it is thought that the prevalence of type 1 diabetes is lower in African populations than in the Western world.

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Introduction

Approximately 171 million people worldwide have diabetes, and this number is increasing.¹ Diabetes mellitus is a chronic illness, characterised by hyperglycaemia resulting from impairments in insulin secretion, defects in insulin action, or both. The classification of diabetes has moved away from a system where the disease was distinguished based on the requirement for insulin therapy, to one based on the pathogenesis of the disease, wherever possible (see Table I).

The correct classification is important because of the different therapeutic options available to treat the different forms of diabetes. Worldwide, the incidence of type 1 diabetes is increasing, with more children being obese on

presentation as a result of the escalating prevalence of obesity in the youth.³ In addition, there is an epidemic of type 2 diabetes in adolescents.⁴ Clinical distinction is difficult, not only because of the overlap in clinical presentation between obese type 2 diabetic patients and obese children with type 1 diabetes, but also as a result of other forms of diabetes present in the age group < 45 years [maturity onset diabetes in the young (MODY) and latent autoimmune diabetes in adults (LADA)]. An educated decision regarding the type of diabetes can be made based on family history and laboratory tests, including tests for autoimmune markers. However, these types of tests are expensive, and are not readily available in resource-poor African countries.

A number of autoantibodies, genes and environmental factors have been shown to be associated with type 1 diabetes. Worldwide, these risk factors have been extensively studied to differentiate type 1 diabetes from other forms of diabetes. The question arises as to whether or not the genetic and autoimmune associations seen in the rest of the world hold true in African type 1 diabetics. In South Africa, and Africa in general, there is sparse information regarding the epidemiology of this disease, and it is poorly characterised in the black population. This review will provide an overview of the epidemiological, immunological and genetic data that have been generated on type 1 diabetes in Africa, especially in the black population.

Table I: Aetiological classification of diabetes mellitus²

Diabetes mellitus
Type 1 diabetes (β cell destruction, usually leading to absolute insulin deficiency) <ul style="list-style-type: none"> • Autoimmune (type 1A) • Idiopathic (type 1B)
Type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance)
Other specific types of diabetes, e.g. genetic defects of β cell function or insulin action, diseases of the exocrine pancreas, or drug- or chemical-induced diabetics
Gestational diabetes (diagnosed during pregnancy)

Type 1 diabetes mellitus

Type 1 diabetes is caused by the autoimmune destruction of the insulin-producing β cells of the pancreas.⁵ The destruction process is marked by infiltration of the pancreatic islets by mononuclear cells, and may take place over a period of many years.⁶ A large proportion (> 80%) of the β cells are destroyed by the time clinical symptoms appear.⁷

In 2000, it was estimated that 171 million adults 20 years of age or older have diabetes.¹ Type 1 diabetes accounts for 5-10% of all cases of the disease. The majority of patients (approximately 40%) are diagnosed and classified with type 1 diabetes within the first two decades of life, making it one of the most common severe chronic diseases of childhood. However, an increasing number of cases are being recognised in older individuals. In the USA, 1:300 children, and as many as 1:100 adults, develop this disease.⁸

There is a large geographical variability in the incidence of type 1 diabetes.⁹ Scandinavia (36.5/100 000 per year in Finland) and the Mediterranean island of Sardinia (36.8/100 000 per year) have the highest incidence rates in the world, while Oriental populations have the lowest rates (0.1/100 000 per year in China).¹⁰ There are few articles in the literature reporting the incidence and prevalence of type 1 diabetes in Africa. Table II summarises the data obtained from African countries.

The incidence of type 1 diabetes changes with age. The incidence increases from birth to 12 years, reaching a peak at 10-14 years of age, before falling to a much lower rate.²² Studies conducted among African populations have shown a peak incidence of type 1 diabetes at 20-29 years of age, which is a decade later than that observed in Caucasian populations.^{12,23} The reasons for this later age of onset in Africans are not known.

In most instances, there is no difference in the incidence of type 1 diabetes in males and females, with the pubertal peak of incidence in females preceding that in males by one to two years.²⁴ In Africa, there seem to be conflicting reports regarding the gender ratios of black patients with type 1 diabetes (see Table II). Studies carried out among Ethiopian and Nigerian type 1 diabetes patients found a two- and threefold higher incidence of type 1 diabetes in males compared to females, respectively.^{12,16} In contrast, a study carried out among black South African type 1 diabetics, and a second study on Sudanese patients, found a slightly higher incidence of female to male patients, although this was not statistically significant.^{18,19,23} A female predominance was shown in Libyan type 1 diabetic patients in the age range 0-14 years, but a male predominance in the age group 15-34 years. When all the patients were taken as a whole, there was a male predominance in the incidence of type 1 diabetes.¹⁵

Table II: The prevalence/incidence of type 1 diabetes in Africa

	Prevalence	Incidence	Male:female ratio	Age range
Algeria	0.27/1 000 ¹¹	8.1/100 000 ¹¹		< 20 years
Ethiopia		2.1/100 000 ¹²	Twice as high in males as in females	0-78 years, with a peak incidence at 25-29 years
Ghana	0.75/1 000 ¹³			
Libya		7.8/100 000 ¹⁴	Excess risk for females vs. males	0-14 years
		9/100 000 ¹⁵	Increased incidence of male to female. Female predominance in group aged 0-14 years, male predominance in group aged 15-34 years.	< 35 years
Nigerian Igbo	0.25-0.46/1 000 ¹⁶		3:1 male:female prevalence ratio	5-17 years
North-West Nigeria	3.1/1 000 ¹⁷		1:0.6 male:female ratio	Age at presentation: 10 \pm 4.5 years
Sudan		10.1/100 000 ¹⁸	Slightly higher in females than males	0-14 years. Peaks at 12 and 14 years in females and males, respectively
	0.95/1 000 ¹⁹		Slightly higher in females than males	7-14 years
Tanzania		1.5/100 000 ²⁰		0-19 years. Incidence increased with age
Tunisia		6.76/100 000 ²¹	No difference	0-14 years. Incidence peaked in group aged 10-14 years.
		6.95/100 000 ²¹	No difference	0-19 years

Autoimmunity

Autoantibodies in type 1 diabetes

Autoantibodies are currently the most frequently used markers for the prediction of type 1 diabetes. The most prevalent autoantibodies are directed at the 65 kDa isoform of glutamic acid decarboxylase (GAD65; 70-80%), the tyrosine phosphatase-like protein (IA)-2 (50-80%), and insulin (IAA; \pm 50% in newly-diagnosed children).²⁵⁻²⁷ Up to 90% of newly diagnosed type 1 diabetic patients have autoantibodies to one or more of these autoantigens. The percentage positivity depends on the age and ethnicity of the patient, as well as the duration of the disease. These autoantibodies can be present in the serum of prediabetic individuals years before clinical diagnosis, and the presence of all three autoantibodies is highly predictive of future type 1 diabetes development.²⁸

There are very limited epidemiological, immunological and genetic data available for the African type 1 diabetes population, especially in southern Africa. Over the past 30 years, there have been approximately 15 publications, the majority from northern Africa, reporting on the presence of autoantibodies in the serum of African type 1 diabetic patients. The majority of papers have only addressed the presence of islet cell antibodies (ICAs).

As seen in Table III, there is wide variation in the frequency of ICAs within Africa.²⁹⁻³⁶ The observed frequencies are lower than those reported in Caucasian type 1 diabetic populations.³⁷ Less than a third of the publications considered the presence of two or more autoantibodies. The prevalence of GAD autoantibodies was studied in 84 Tunisian type 1 diabetic children.³⁶ With increasing duration of type 1 diabetes, the prevalence of GAD autoantibodies decreased: 84.6% of children with newly-diagnosed diabetes (< 6 months) were positive for GAD autoantibodies, as opposed to only 29.41% in those with a longer duration of disease (> 5 years). In another study, 47 type 1 diabetes patients from Cameroon were screened for GAD and IA-2 autoantibodies.³⁸ The mean disease duration was 3.3 years. Sixteen patients and three patients were GAD- and IA2-autoantibody-positive, respectively. Similarly, a study carried out in Tanzania revealed lower frequencies of GAD and IA-2 autoantibodies compared to Caucasian type 1 diabetic patients.^{37,39} Only one paper looked at the frequency of all four autoantibodies in 86 newly diagnosed type 1 diabetic children from Tunisia.³¹ The authors found that 78 (90.7%) children were positive for one or more autoantibody. Only three papers were identified that reported the screening of black South Africans for the presence of disease-associated autoantibodies. In the first paper, ICAs were found in over a third of black and Indian South African patients.⁴⁰ The

Table III: The prevalence of type 1 diabetes associated autoantibodies in African populations

Study population	Number and type of patients	ICA+	GAD65+	IA-2+	IAA+
Ethiopia ²⁹	43 newly diagnosed black	39%	-	-	-
Tunisia ³⁰	175 black	45.1%	-	-	-
Tunisia ³¹	86 newly diagnosed black	57%	65.1%	43%	50%
Sudan ³²	46 newly diagnosed black	63%	-	-	-
Sudan ³³	96 black	41.7%	-	-	-
Nigeria ³⁴	68 black	5.9%	-	-	-
Tanzania ³⁵	35 newly presenting black	8.6%	-	-	-
Tunisia ³⁶	84 black	21.4%	51.2%	-	-
Cameroon ³⁸	47 black	-	34%	6.4%	-
Tanzania ³⁹	94 black	-	21.3%	12.8%	-
South Africa ⁴⁰	47 black	36.2%	-	-	-
	34 Indian	32.4%	-	-	-
South Africa ⁴¹	100 black	-	44%	-	-
South Africa ⁴²	43 black	-	33%	-	-
	17 Caucasian	-	67%	-	-
America ³⁷	113 black	58%	54%	38%	20%
	117 Caucasian	77%	73%	65%	35%

remaining two studies examined the presence of GAD autoantibodies, and found a lower prevalence in black type 1 diabetic patients, compared to Caucasian type 1 diabetic patients.^{41,42}

Autoantibodies and latent autoimmune diabetes in adults

GAD65 and insulin autoantibodies were also found in 5-10% of patients classified with type 2 diabetes.^{43,44} Initially, these patients have residual β cell function, sufficient to prevent the development of acute metabolic decompensation (ketosis) for many years. However, the β cell mass declines over time, thus necessitating insulin treatment.⁴⁵ This slowly progressing form of type 1 diabetes is termed LADA, or type 1.5 diabetes.^{44,46} The Immunology of Diabetes Society has proposed the following definition for LADA: patients must be ≥ 30 years of age, be positive for at least one autoantibody, and require no insulin within the first six months following diagnosis.

There is sparse information on the presence or absence of LADA in Africa. One reason for this may be the difficulty in classifying the different types of diabetes. In a study conducted in 124 type 2 diabetic patients from Nairobi, it was found that 79% were "true" type 2, 5.7% were LADA, 12.1% were type 1B, and 3.2% were type 1A diabetics.⁴⁷ Similar findings were reported in a study of 103 non-insulin-requiring diabetic patients from Ghana.¹³ Seventeen (16.5%) of the non-insulin-requiring patients were positive for ICA and/or GAD and/or IAA, and the prevalence of LADA in this group was 13.5%.¹³ Thus, clinical judgement alone cannot be used to classify patients, and may be one of the reasons for the poor glycaemic control seen in a number of diabetic patients.

Susceptibility to type 1 diabetes mellitus

The rapid increase in the incidence of type 1 diabetes (3.9% average annual increase in Europe over the period 1989-2003) cannot be accounted for by genetics alone.⁴⁸ A seasonal variation in the incidence of type 1 diabetes has been observed. There is a decline during the warm summer months.⁴⁹ However, this seasonal pattern only appears to occur in older children and adolescents, suggesting that factors triggering diabetes may be related to school attendance or viral infections.⁵⁰

In Africa, as in the rest of the world, there are confounding reports as to whether or not viruses are a significant factor in the aetiology of type 1 diabetes. A study of 40 insulin-treated Nigerian diabetics did not show any association of Coxsackie B1, mumps, rubella and enterovirus group antigen with type 1 diabetes. The non-diabetic control

samples (who were matched for age, sex and social status) had significantly higher levels of Coxsackie A virus compared to the diabetic patients.⁵¹ Thus, in this group, previous exposure to these viruses is not a trigger of type 1 diabetes. A second study conducted on 40 newly diagnosed type 1 diabetic patients (> 1 -year duration of disease; Group 1), 30 type 1 diabetic patients (< 1 -year duration; Group 2) and 30 healthy non-diabetic children from Egypt showed a significant increase in the evidence of viral infection in Group 1 and Group 2 vs. the control subjects.⁵²

Genetic susceptibility

Type 1 diabetes is a heterogeneous and polygenic disorder. There are currently more than 40 gene loci that have been linked with influencing type 1 diabetes risk. The two major susceptibility regions that have been identified are IDDM1, the major histocompatibility complex region on chromosome 6p21, and IDDM2, the insulin gene region on chromosome 11p15.5.⁵³

The best studied is IDDM1, which contains the human leucocyte antigen (HLA) genes that code for HLA class II antigens. Fine mapping of this locus suggests that two HLA haplotypes, DR3 and DR4, are strongly associated with type 1 diabetes susceptibility.⁵⁴ The vast majority (90%) of type 1 diabetics have either DR3,DQ2 (DQ2 = DQA1*0501, DQB1*0201) or DR4,DQ8 (DQ8 = DQA1*0301, DQB1*0302) haplotypes, whereas 40-50% of most non-diabetics have one or the other of these haplotypes. Between 30-50% of patients with type 1 diabetes are heterozygotes with DR3,DQ2/DR4,DQ8 compared with only 2.4% of the general population.

A number of studies have analysed the frequency of HLA antigens in African type 1 diabetic patients. One study conducted in Algerian type 1 diabetic patients found a strong association of DR3 with type 1 diabetes. DR4 was found to be equally distributed in patients and controls (21% vs. 28.4%). However, the DR3 and DR4 heterozygous allele was present more frequently in diabetics.⁵⁵ A second study found a higher frequency of the haplotypes (DR3DQ2 or DR4DQ8) in diabetics (85%) vs. controls (34%), and 42% of the patients had the heterozygous haplotype DR3DQ2/DR4DQ8.⁵⁶ A third study carried out in western Algeria, where there is a high rate of consanguineous marriages, failed to show an association of DR3 with diabetes, but there was an association with DR4 and DR3/DR4 antigens.⁵⁷

Several studies have been performed on the diabetic population of Tunisia. All studies showed a positive association with DR3 and DR4, and a strong association of the heterozygote genotype DR4-DQw8/DR3-DQw2 to type 1 diabetes.⁵⁸⁻⁶⁰ DR2 and DR5 were confirmed to play

a protective role in this population group.⁵⁸ Similarly, Abid Kamoun et al have shown the DRB1*01501 DQB1*0602 and DRB1*11 DQB1*0301 haplotypes to be protective.⁶⁰

The majority of studies that have focused on the HLA antigens (typed serologically) have been carried out in South Africa. In the first study, conducted in 1980, Briggs et al, found no increase in the frequency of B8 and B15, and no decrease in B7 in the 25 Xhosa type 1 diabetic patients.⁶¹ This is in contrast to what was observed in Caucasian type 1 diabetic patients. Hammond et al did find an increase in the frequency of B8 and B14 in 57 black South African diabetic patients.⁶² In 1983, Shires et al compared the frequency of HLA antigens in 72 Caucasian, and 53 black, type 1 diabetic patients.⁶³ HLA A1 and B8 antigens were significantly increased, while A3 and B17 antigens were reduced in the Caucasian diabetic group. Only HLA B8 was increased in the black diabetic sample. Two studies were conducted by Omar et al, in which the HLA A, B and C antigen status were determined, in addition to DR typing, in black and Indian type 1 diabetic patients from South Africa.^{64,65} In the black patients, the frequency of DR4 was significantly higher compared to in the control subjects, and DR3/DR4 heterozygosity was associated with a greater relative risk for developing disease, compared to the presence of DR3 alone. Indian diabetic patients showed a significant increase in the frequency of B8, Aw24 and DR3 HLA antigens, compared to controls. A strong association was also observed with DR4 among patients of north Indian origin. A study conducted on black South African and coloured South African type 1 diabetic patients, showed a weak association with DRw9 in the black population, but failed to show any other associations commonly seen in black American type 1 diabetic patients. The coloured patients failed to show an association with B8 and DR3, but did have an increased frequency of DR4 and a decreased frequency of DR2, commonly seen in Caucasian populations.⁶⁶

The latest South African study reported in the literature was published in 2001. In this study, Zulu diabetics [typed by polymerase chain reaction (PCR) with sequence-specific primers] showed the presence of the common susceptibility antigens: DR3, DR4, DQ2 and DR9.⁶⁷ These findings were similar to those reported from other studies. One study carried out in Nigeria did not show an association of type 1 diabetes with DR4. The reason for this may be that DR4 correlates with an early age of onset in Caucasian type 1 diabetic patients, and the Nigerian patients in this study had an age of onset > 20 years.⁶⁸

Although susceptibility to type 1 diabetes is strongly associated with certain HLA alleles, other genetic loci also play a role in the triggering and/or development of the

disease. The IDDM2 locus accounts for about 10% of the susceptibility toward type 1 diabetes.⁶⁹ This locus maps to a variable number of tandem repeats (VNTR), or minisatellites, upstream of the insulin gene.⁵³ The short class I VNTRs (30-44 repeats) predominate (70%) in Caucasians. The remaining alleles tend to fall into the longer class III category. The intermediate lengths (class II) are rare. Class I VNTR alleles predispose to type 1 diabetes, whereas the class III alleles have a dominant protective effect.⁶⁹ The presence of at least one class III allele is associated with a threefold reduction in the risk of developing type 1 diabetes.⁷⁰

Undlien et al studied 488 type 1 diabetics from three different ethnic groups, Tanzanian blacks, Norwegian Caucasians and Japanese Orientals, to determine whether there was an association between polymorphisms in the insulin gene and the occurrence of type 1 diabetes.⁷¹ The presence of insulin gene polymorphisms conferred susceptibility in the Caucasian patients, as well as the Tanzanians. However, this tendency was not statistically significant. No association was observed in the Japanese population group.

Findings of the majority of genetic studies conducted in Africa are in agreement with those from studies carried out in Europe and America, namely that DR3 and DR4 are more common in type 1 diabetic patients, and that the heterozygote haplotype, DR3/DR4, is strongly associated with type 1 diabetes. A number of studies also support the protective role of DR2 and DQB6. There are also some haplotypes that are unique to different regions in Africa. Larger studies are required among African populations to determine which haplotypes are suggestive of an increased risk of type 1 diabetes development in the different ethnic groups. Similarly, an insufficient number of studies have been carried out to determine whether or not there is an association between the different susceptibility genes and type 1 diabetes in Africa.

Conclusion

Little is known about the autoimmune role in the pathology of disease in African populations. One study has shown a lower prevalence of GAD autoantibodies in black South Africans, compared to data obtained from Caucasian type 1 diabetic patients.⁴² There is some evidence of ethnic differences in the autoimmune response. This needs to be further investigated, using the measurement of GAD, IA-2 and insulin autoantibodies. The latter two autoantibodies have never been investigated in the South African black population.

It should also be borne in mind that the prevalence of type 1 diabetes is thought to be lower in Africans than Europeans. Therefore, there may also be significant ethnic differences

in both the aetiology and pathology of the disease.⁷² Further research into the aetiology and pathology of type 1 diabetes in Africa needs to be conducted, as the information will help to characterise diabetes in the different population groups. This will provide important information on the role of the immune system in the disease aetiology, particularly in black Africans, for whom there are currently little such data.

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