(i)

T I T L E

AUTOIMMUNE PROFILE IN INSULIN DEPENDENT

DIABETES MELLITUS

AT KENYATTA NATIONAL HOSPITAL

DR. S.K. SHARIF M.B., Ch.B.

A dissertation presented as part of fulfillment
for the degree of Master of Medicine (Medicine)
of the University of Nairobi.

DECLARATION

This dissertation is my original work.
and has not been presented for a degree in
any other University.

Signed : ------------------------

Dr. S.K. Sharif, MBChB (Nairobi)

This dissertation has been submitted for
M. Med (Medicine) examination with our approval.

Signed : ------------------------

Professor T. Bowry, MBChB, MRCPath
Head, Department of Immunology
College of Health Science
University of Nairobi.

Signed : ------------------------

Dr. A.O.K. Obei, MBChB, MRCP, PhD.
Snr. Lecturer in Medicine &
Head, Division of Pharmacology &
Therapeutics, Department of Medicine
College of Health Sciences
University of Nairobi.

C O N T E N T S

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A C K N O W L E D G E M E N T S

S U M M A R Y

131   patients with IDDM attending K.N.H. were studied.
The mean age of onset of IDDM was 20.1 years.   There
was a male predominance with M:F ratio of 1.4:1   There
was a low prevalence of IDDM among first degree
relatives of diabetic probands.   Definitive history of
viral infection preceding the onset of IDDM was found in
one patient.   None of the patients had thryroglobulin
antibodies;   thyroid microsomal antibodies were found in
0.7% of the patients.   Parietal cell antibodies were
found in 4.6% of the patients.   Islet cell antibodies
were found in 3.7% of patients with IDDM.   The prevalence
of autoantibodies in Kenyan Africans with IDDM is much
lower when compared with Caucasians and Black Americans
with IDDM.   In view of the low prevalence of autoantibodies
in Kenyan Africans with IDDM, primary autoimmune diabetes
mellitus is considered rare in Kenyan Africans with IDDM.

I N T R O D U C T I O N

Diabetes mellitus is a common disease affecting approximately
2 - 3% of the population in developed countries (1). Diabetes
mellitus is defined as a state of chronic hyperglycaemia. The
hyperglycaemia may be due to lack of insulin or to an excess of
factors and hormones such as growth hormone, glucocorticoids,
glucagon and somatostatin that oppose the action of insulin.
Several studies have shown that a wide variety of environmental
and genetic factors may cause the diabetic state. There are
also different clinical manifestations of diabetes mellitus.
Diabetes mellitus is not a single disease, rather, it may be
viewed as an heterogenous group of diseases, the common
denominator being chronic hyperglycaemia. Recognition of the
heterogeneity of diabetes mellitus has prompted the Diabetes
Data Group of the National Institutes of Health (NDDG) U.S.A.
to propose a new classification based on clinical and aetiological
grounds (2). The NDDG classification of diabetes mellitus was
accepted by the World Health Organization in 1980 (3).

Type 1 or insulin dependent diabetes mellitus (IDDM) is
characterised by hyperglycaemia, dependence on insulin to
sustain life, florid symptoms, younger age of onset and
tendency to develop ketoacidosis without insulin therapy. The
mere use of insulin in the treatment of a diabetic is not
adequate in itself to fulfil the classification requirement.
A history of clinical onset with ketoacidosis is the strongest
supporting evidence. However, this may not always be available.
Type II diabetes or non-insulin dependent diabetes mellitus
(NIDDM) defines a group of patients who do not require insulin.
It usually occurs in older, obese persons and is characterised

by the absence of ketoacidosis though they may become ketotic
during acute medical or surgical stress. A distinct subgroup
known as maturity onset diabetes mellitus of youth (MODY) may
be diagnosed in patients in their teens (4). Though these
patients are usually treated with insulin, they are able to
survive without it (5).

Genetic predisposition, autoimmunity and environmental factors
acting independently or together have been implicated in the
pathogenesis of IDDM (6). It has long been recognised that
insulin dependent diabetes mellitus shows a strong familial
tendency. Tattersall and Pyke in their study of monozygotic
twins found a 93% concordance rate for adult onset disease
(greater than age 40 at diagnosis) and a 50% concordance rate
for juvenile onset disease (7).

This suggests that genetic factor tends to predominate in
NIDDM but not in IDDM. Another approach to the study of
inheritance of IDDM apart from twins studies is human leukocyte
antigens (HLA) typing. These cell surface antigens are associated
with rejection of tissue transplants. The genes coding for HLA
antigens -A, -B, -C, and -DR (D - related) occupy four loci
along the short arm of chromosome 6 (8, 9).

Initial population studies in IDDM found a higher proportion
of HLA antigens B8 and B15 (10,11). Subsequent studies have
demonstrated that in Caucasian populations an increased relative

risk for developing IDDM is associated with HLA DR3 and DR4 (12,13).
Current evidence suggests that the strongest association of IDDM
lies with HLA DR3 and HLA DR4 (14). The previously reported
findings with respect to HLA B antigens are secondary to linkage
disequilibrium within the HLA system (14). HLA B8 is in linkage
disequilibrium with DR3 while HLA B15 is in linkage disequilibrium
with DR4 (14). Though most of the studies on HLA antigens in IDDM
have been in Caucasian populations in Europe and North America, there
is one study which reports an association between HLA DR3 and HLA DR4
in American Blacks with IDDM (15).

HLA studies in siblings of patients with IDDM have shown a
statistically significant association between the sharing of HLA
identical haplotypes and development of IDDM (16, 17). Rubinstein
(16) studied HLA types in 31 families having one or more children
with type I diabetes mellitus. In 23 families, 50% of the HLA
identical siblings were diabetic whereas only 6% of the non-identical
siblings were diabetic. Gorsuch (17) in his study of 288 siblings
of 160 patients with IDDM taking part in Barts Windsor Family Study
found that statistically significant number of HLA identical
siblings developed IDDM. Ginsberg - Fellner et al (18) in their
study of IDDM found that there was an increased risk of developing
IDDM in siblings of patients with IDDM if they were HLA identical.
These studies support the concept that the genetic susceptibility
to IDDM is HLA linked.

Autoimmunity was implicated as an aetiological factor in
pathogenesis of type I diabetes mellitus when it was noted
that there was a higher prevalence of insulin dependent

diabetes mellitus in patients with Addison's disease as
compared with normal population (19). Subsequent studies
showed that there was a significantly higher prevalence of
primary hypothyroidism in patients with IDDM as compared to
NIDDM (20). Other investigators also noted that there was
an increased incidence of thyroid autoantibodies and gastric
parietal cell antibodies in patients with IDDM as compared
with normal controls (21).

Antibodies against the cytoplasm of pancreatic islet cells, as
detected by indirect immunofluorescence using sections of blood
group O human pancreas were first isolated in 1974 in diabetic
patients with organ specific autoimmune disease (22, 23).
Subsequent studies showed a high prevalence of islet cell
antibodies in newly diagnosed cases of type I diabetes mellitus
(24, 25). The prevalence of islet cell antibodies falls
rapidly; 60% of newly diagnosed cases of type I diabetes
mellitus have islet cell antibodies as compared with 15 - 20%
of patients with type I diabetes mellitus of more than two years
duration (24). About 10 - 15% of patients with type I diabetes
mellitus have persistent islet cell antibodies for many years
(26). Islet cell antibodies have also been detected before
clinical onset of disease by as many as five years (27). Islet
cell antibodies have also been detected in unaffected first
degree relatives of patients with IDDM more frequently than in
normal controls (17). Islet cell antibodies have also been
helpful in detecting apparently normal persons who are at risk
of developing IDDM (28, 29, 30). A separate species of islet
cell antibodies which fixes complement has been identified (29).

These complement fixing islet cell antibodies are distinct from
the conventional islet cell antibodies and are more closely
related to the onset of clinical disease than conventional
islet cell antibodies (29).

Viruses have been implicated in the pathogenesis of IDDM. The
most direct evidence of the role of viral infection has been
the Coxsackie B4 virus which was isolated from the pancreatic
tissue of a child who died with meningoencephalities and new
onset diabetes mellitus (31). The isolated virus was then
injected into a susceptible species of mice. This resulted
in damage to the beta cells of the islet of Langerhans of the
pancreas with subsequent diabetes mellitus (31). Gamble (32)
reported that within the first three months of the onset of
IDDM, higher titres of neutralising antibodies to Coxsackie B4
virus were found as compared to those in normal subjects or
in patients with diabetes mellitus of a duration of longer
than three months. Encephalomyocarditis (EMC) virus has been
shown experimentally to produce diabetic like state in mice
(33). Venezuelan equine virus has also been shown to produce
a diabetic like state in mice (34). However, only a few strains
of mice develop a diabetic like disease after viral infections
whereas other strains seem to be resistant to the development
of diabetes - like state. This suggests that there is a
genetically determined susceptibility to develop diabetes -
like state (33). Gamble described a seasonal incidence of
insulin dependent diabetes mellitus in patients up to the age
of 19 most marked in October with a smaller peak in July (35).
These peaks showed a significant positive correlation with

annual prevalence data for Coxsackie B4 virus but not for other
types of viral infections (35). However, other workers have not
been able to confirm these findings (36). There have also been
several reported cases of IDDM following mumps infection (38, 39).

Chemicals may be responsible for diabetes. Streptozocin when
injected into some strains of mice leads to pancreatic islet
cell damage and hyperglycaemia (40). N-nitroso derivatives
which are food additives have been shown to induce diabetes
in offspring of mice which were fed large amounts of N-nitroso
compounds (41). However, there is no direct evidence that
N-nitroso compounds are important in pathogenesis of type I
diabetes mellitus in human beings (41).

There have been several reports that autoimmunity may be an
important aetiological factor in the pathogenesis of IDDM
in Caucasians (42, 43). However, studies from Africa are
scanty. One study from West Africa in patients with new
onset diabetes mellitus showed a low prevalence of islet cell
antibodies and organ specific antibodies (44). Studies from
Black Americans with IDDM indicate that they have a lower
prevalence of thyroid auto antibodies and islet cell antibodies
when compared with Caucasian populations with IDDM (45). These
differences among the various population groups prompted this
study with the following objectives.

O B J E C T I V E S

1.   Study the prevalence of islet cell antibodies in
      Africans with insulin dependent diabetes mellitus
      (IDDM) attending the Kenyatta National Hospital.

2.   Study the prevalence of thyroid microsomal, thyro-
      globulin and parietal cell antibodies in Africans
      with IDDM attending the Kenyatta National Hospital.

3.   Study the prevalence of islet cell antibodies in
      non diabetic hospital controls.

PATIENTS, METHODS AND MATERIAL

PATIENT SELECTION: This study was carried out in African patients
with IDDM according to NDDG criteria (2) who were attending the
Kenyatta National Hospital between September 1982 and July 1984.
Patients were included in the study if they had IDDM of less than
five years duration and were not on cortcosteroids for any other
disease.   Due to financial and technical constraints, the sample
size was limited to 131 patients.

The age of the patient and the duration of the disease from the
onset of symptoms was noted.   Detailed history of diet. alcohol
consumption and family history of IDDM was taken.   The clinical
and laboratory protocol employed for the patients is given in
Appendex A.

CONTROL GROUP: The control group consisted of 51 non diabetic,
age and sex matched hospital patients.   All the controls
had a random blood glucose of less than 8.0 mmol/L.

BLOOD COLLECTION: 10 ml. of blood was collected from patients
by venepuncture and the serum was stored at $-70^{\circ}C$.

LABORATORY STUDIES:

Thyroid microsomal antibodies were detected using haemagglutination
with tanned turkey erythrocytes using a commercial kit (Thymune
M - Welcome Reagents) as described (46).   The test was considered
positive if there was haemagglutination in a dilution of 1:40
and onwards.

Thyroglobulin antibodies were detected using haemagglutination
with tanned turkey erythrocytes using a commercial kit (Thymune
T - Welcome Reagents) as described (46). The test was considered
positive if there was haemagglutination in a dilution of 1:40
and onwards.

Islet cell antibodies were detected by indirect immunofluorescence
using unfixed, cryostat frozen sections of blood group O human
pancreas as described by Bottazzo (22). The result (scale 0 to +++)
was considered positive if the test sample showed one plus (+)
reaction to endocrine cells.

STATISTICAL ANALYSIS

Statistical analysis was done using mean and statistical
significance was calculated using Student t test.
Statistical significance was assumed if the P value was
equal to or less than 0.05.

RESULTS

131 patients were studied. There were 77 males and 54 females,
a male to female ratio of 1.4 to 1.   The age distribution of
patients studied is shown in Figure 1. The peak age was 10 -
30 years, the mean age was 21.8 years. The age distribution at
the onset of IDDM is shown in Figure 2. The peak age of onset
of IDDM was between 10 - 30 years. The mean age at the onset
of IDDM was 20.1 years. The duration of the disease from the
onset of symptoms is indicated in Table 1.   49% of the
patients studied had disease for less than one year.

Family history from 131 diabetic probands revealed that they
had 60 siblings. None of the 30 siblings available at the
time of the study had IDDM from history.   30 siblings were
not available at the time of the study due to separation
from their parents or due to death; the cause of death could
not be ascertained in the dead siblings. Of the 151 parents
of diabetic probands available at the time of the study only
one parent had IDDM.   111 parents were not available at the
time of the study.

Detailed history about alcohol revealed that none of the
patients studied had significant (more than three bottles
of beer per day) history of alcohol consumption.

Autoantibody profile :   The autoantibody profile of patients with
IDDM and non - diabetic control is shown in Table 2.   None of the
non - diabetic hospital controls had thyroid microsomal or
thyroglobulin antibodies.   0.7% of the patients with IDDM had
thyroid microsomal antibodies and none had thyroglobulin
antibodies.   The differences in these two groups were not
significant (P > 0.05).   4.6% of patients with IDDM had
parietal cell antibodies as compared with 1.9% in the control
group. This difference was not considered statistically
significant (P > 0.05).

Due to technical constraints in obtaining fresh human pancreas,
islet cell antibody could only be done in 80 patients with IDDM
and 51 controls.   None of the controls had islet cell anti-
bodies.   3.7% of the patients with IDDM had islet cell anti-
bodies.   The results in these two groups did not reach a
level of statistical significance (P > 0.05). The prevalence
of islet cell antibodies in relation to the duration of the
disease is indicated in Table 3.   5.8% of the patients with
IDDM of less than one year's duration had islet cell antibodies
as compared with 7.1% in patients with disease duration of
between one and two years which is not statistically significant.
None of the patients with IDDM of more than two year's duration
had islet cell antibodies. Age, sex and autoantibody profiles
of patients who had islet cell antibodies is shown in Table 4.

FIGURE I

AGE DISTRIBUTION OF 131 PATIENTS

WITH IDDM

AGE IN YEARS
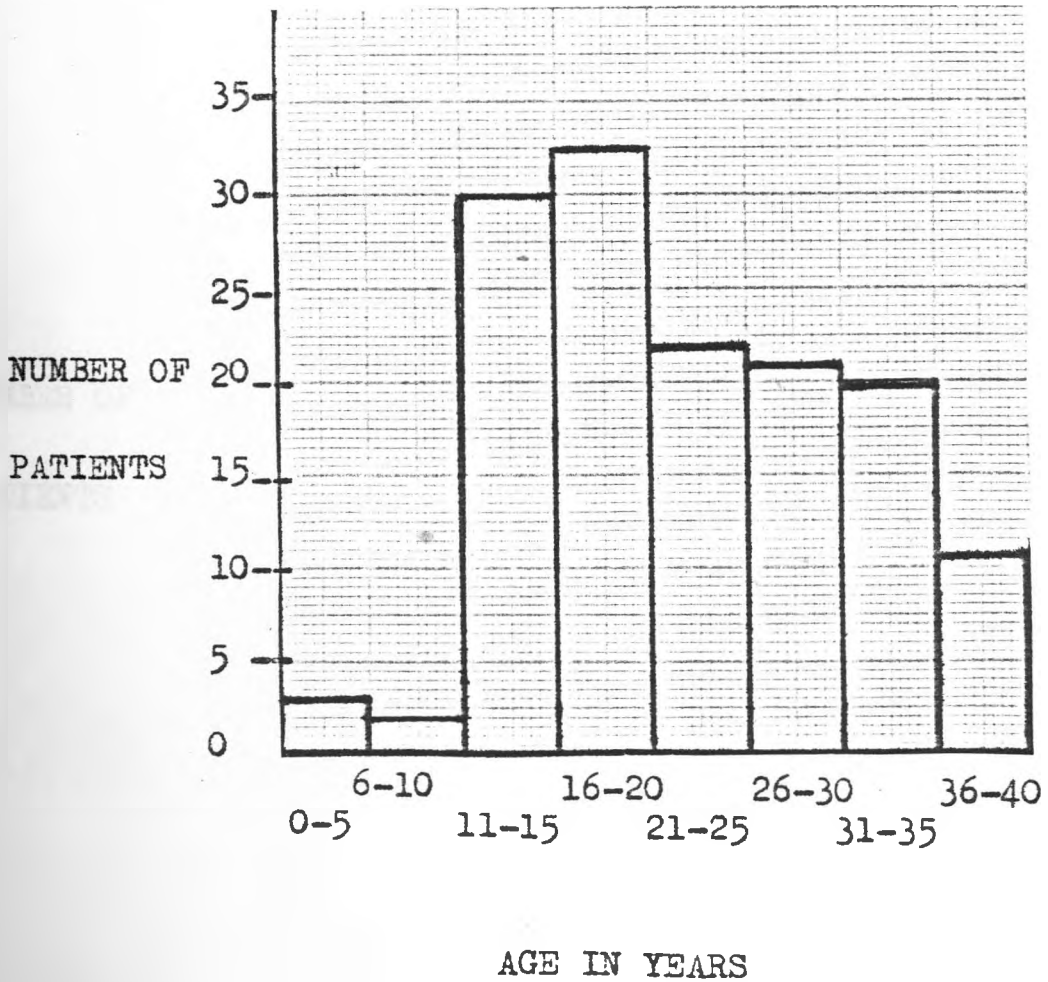
FIGURE 2

AGE DISTRIBUTION AT THE ONSET

OF IDDM IN 131 PATIENTS

NUMBER OF

PATIENTS

AGE IN YEARS
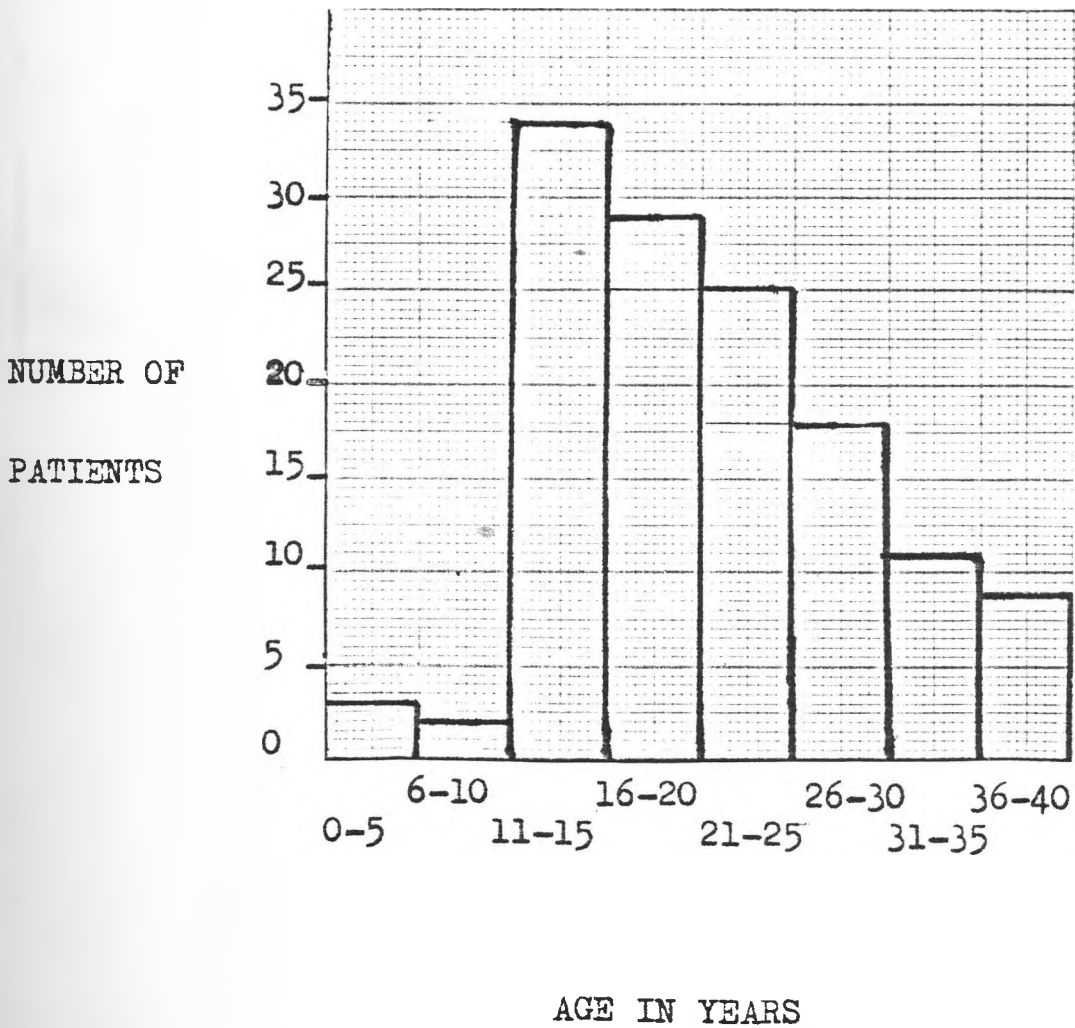
TABLE 1

Duration of the disease from the onset of symptoms.

	Duration of IDDM (in months)				
Sex of patients	0 – 12	12 – 24	24 – 36	36 – 48	48 – 60
Males	30	16	12	13	6
Females	34	5	4	5	6
Total Number	64 (49%)	21 (12%)	16 (12%)	18 (14%)	12 (9%)

TABLE   2

AUTOANTIBODIES IN PATIENTS WITH IDDM AND NON DIABETIC
HOSPITAL CONTROLS.

	ANTIBODY	TMA	TGA	PCA	ICA
IDDM	M	O	O	3	I
	F	1	0	3	2
	TOTAL	1/131	0/131	6/130	3/80
	P	NS	NS	NS	NS
CONTROL	M	0	0	1	0
	F	0	0	0	0
	TOTAL	0/51	0/51	1/51	0/51
	P	NS	NS	NS	NS

KEY :

    TMA   :   Thyroid microsomal antibodies
    TGA   :   Thyroglobulin antibodies
    PCA   :   Parietal cell antibodies
    ICA   :   Islet cell antibodies
     NS   :   Not significant

TABLE 3

Prevalence of islet cell antibodies in 80 cases of
IDDM in relation to duration of the disease.

	DURATION OF IDDM IN MONTHS				
	0–12	12–24	24–36	36–48	48–60
Islet cell antibodies positive	2 (5.8%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)
Islet cell antibodies negative	32	13	14	6	12
Total	34	14	14	6	12

TABLE 4

AGE, SEX AND ANTIBODY PROFILES OF IDDM PATIENTS WITH
ISLET CELL ANTIBODIES.

AGE	SEX	TMA	TGA	PCA
22 years	F	–	–	–
22 years	M	–	–	–
36 years	F	+ve	–	–

KEY :

TMA	:	Thyroid microsomal antibodies
TGA	:	Thyroglobulin antibodies
PCA	:	Parietal cell antibodies

TABLE 5

PREVALENCE OF AUTOANTIBODIES IN VARIOUS POPULATIONS WITH IDDM.

STUDY	POPULATION	TMA	TGA	PCA	ICA*
Lendrum (24)	Caucasians	12%	-	-	38%
Irvine (25)	Caucasians	-	-	-	22%
Neufield (45)	Caucasians	20%	-	8.5%	36.1%
Neufield (45)	U.S. Blacks	4%	-	10%	22%
Riley (52)	Caucasians	20.1%	-	7.8%	-
Riley (52)	U.S. Blacks	5.5%	-	9.4%	-
Del Prete (59)	Caucasians	-	-	-	24.2%
PRESENT STUDY	Kenyan Africans	0.7%	0%	4.6%	3.7%

KEY :

TMA : Thyroid microsomal antibodies

TGA : Thyroglobulin antibodies

PCA : Parietal cell antibodies

ICA*: Islet cell antibodies irrespective of the duration of the disease.

D I S C U S S I O N

All the patients studied had abrupt onset of symptoms, random
blood glucose of more than 14.0 mmol/L on more than three
occasions and at least one documented episode of diabetic
ketoacidosis. Their selection criteria would satisfy the
NDDG criteria of type I diabetes mellitus or insulin
dependent diabetes mellitus (2). The same selection criteria
would effectively exclude maturity onset diabetes of the young
described by Tattersall and Fajan (5).

AGE AND SEX : The peak age of onset was between 10 - 30 years
and the mean age of onset of IDDM was 20.1 years. This is a
much higher age of onset than reported by other investigators
(18, 47). Ginsberg - Fellner et al (18) in their study found
that the mean age of onset of IDDM was 13.7 years. The Pittsburg
study found that the mean age of onset of IDDM was 7.8 years (47).
Neufield (45) in his study found that the mean age of onset of
IDDM in U.S. Caucasians was 8.1 years and 10.2 years in U.S.
Blacks. The reason for the high age of onset of IDDM in this
study is not clearly known but may be due to the fact that most
of the patients included in the study were attending the
Diabetic Clinic which is manned by physicians while some
paediatricians follow few diabetic children in the paediatric
clinics. A male predominance was noted in this study. A
male predominance has also been noted by some investigators (17),
however, male predominance is not a universal finding in studies
of IDDM. The Pittsburg study found an equal male to female
ratio (47). However, it must be noted that the male
predominance in our study may be due to a bias in the number of

females attending the Diabetic Clinic which is situated in Nairobi. It is possible that many women may be attending hospitals near their homes in rural areas and thus be missed in this study.

ALCOHOL AND DIET : This study reveals no association between alcohol consumption and IDDM in Kenyan Africans. Mngola (49) has recently described a ketosis prone diabetic state in patients over the age of twenty associated with high consumption of a local alcoholic brew. It is very unlikely that any of the patients included in this study had the pancreatic diabetes described by Mngola. Detailed dietary history revealed that Cassava consumption was uncommon in patients with IDDM. Cassava consumption has been associated with Pancreatic Fibrosis Calcification Syndrome (PFC Syndrome) (49). Pancreatic Fibrosis Calcification Syndrome has been described in several countries and is characterised by recurrent abdominal pain, onset of diabetes at a young age, male predominance, large insulin requirements for control and resistance to develop ketoacidosis on insulin withdrawal. In view of the lack of cassava consumption and the tendency of the patients to develop ketoacidosis in this study, it is most unlikely that any of the patients included in this study had PFC Syndrome.

RELATION TO FAMILY HISTORY : Family studies in Caucasians with IDDM showed that there is an increased prevalence of IDDM among first degree relatives of patients with IDDM. Gorsuch (50) in his study of first degree relatives of patients with IDDM found that 3.5% of the parents and 5% of the siblings of IDDM probands developed IDDM. The risk of developing IDDM in Gorsuch's study (50) was greatest among HLA identical siblings, suggesting that the genetic susceptibility to IDDM is HLA linked. Warram et al (51) have also reported higher prevalence of IDDM among off-spring of diabetics, 1.3% of the offspring of women with IDDM and 6.1% of the offspring of men with IDDM were diabetic by the age of 20. In our study only one parent of a diabetic proband had IDDM. None of the offspring of the diabetic patients had IDDM. This low prevalence of IDDM among first degree relatives of patients with IDDM in this study may be due to the fact that in many cases definitive history of IDDM among first degree relatives could not be ascertained due to unavailability of first degree relatives either because of separation or death. The other factor may be that this was a short term study and may have missed many first degree relatives who were at risk of developing IDDM but at the time of study did not have IDDM. The low prevalence of IDDM among first degree relatives of patients with IDDM needs to be confirmed by further long term studies.

THYROID AUTOANTIBODIES :   None of the patients with IDDM in this study had thyroglobulin antibodies and only 0.7% of the patients with IDDM had thyroid microsomal antibodies.   The prevalence of thyroid autoantibodies in this study is much lower than reported by other investigators (24, 25) (Table 5). Lendrum (24) in his study of 750 patients with IDDM found that 12% of the patients with IDDM had thyroid microsomal anti- bodies.   He also found that the prevalence of thyroid microsomal antibodies increased with age and duration of the disease.   Irvine (25) in his study of 1032 diabetics found that there was an increased prevalence of thyroid autoantibodies when compared with normal controls and patients with NIDDM.   Neufield (45) in his study of IDDM found that Caucasians with IDDM had significantly higher prevalence of thyroid microsomal antibodies as compared with Black Americans with IDDM and normal controls.   20% of Caucasians with IDDM in Neufield's study had thyroid micro- somal antibodies as compared with 4% of Black Americans with IDDM.   Riley (52) in his study has reported that Black Americans with IDDM have a lower prevalence of thyroid micro- somal antibodies (5.5%) as compared with 20.1% in Caucasians with IDDM.   This difference was considered statistically significant.   Several studies have shown that there is also an increased prevalence of thyroid autoantibodies among relatives of patients with IDDM (18, 53).   Ginsberg - Fellner et al (18) in thier study showed that 9.7% of first degree relatives of patients with IDDM had evidence of autoimmune thyroid dysfunction and 48% of patients with IDDM had evidence of autoimmune thyroid dysfunction as manifest by thyroid

microsomal antibodies or thyroglobulin antibodies. Fialkow
et al (53) found a 23% prevalence of thyroid autoimmunity in
first degree relatives of patients with IDDM. A low
prevalence of thyroid autoantibodies in patients with IDDM
was found in this study despite using a more sensitive assay
than used in other studies (46). Though it is often suggested
that Black populations have a lower propensity to form organs
specific autoantibodies, Bowry (54) in her study of thyrotoxicosis
in Kenyan Africans found that the commonest cause of thyro-
toxicosis was Graves' disease and thyroid microsomal antibodies
were found in 54.2% of patients with Graves' disease indicating
that Kenyan Africans have the same propensity to develop
thyroid autoantibodies in thryotoxicosis. Thus the low
prevalence of thyroid autoantibodies in this study cannot be
solely due to reduced propensity to form organ specific
autoantibodies as suggested (45, 52). The low prevalence of
thyroid autoantibodies in this study does confirm the suggestion
of Gorsuch (55) who found that the presence of thyroid antibodies
in healthy siblings was independent of HLA haplotypes possessed
by the IDDM proband and suggested that the genes controlling
the production of thyroid autoantibodies are different from
those controlling the susceptibility to IDDM.

PARIETAL CELL ANTIBODIES : The prevalence of parietal cell
antibodies among Kenyan Africans with IDDM in this study was
4.4%. Riley (52) in his study found that 9.4% of Black
Americans with IDDM had parietal cell antibodies while 7.8% of
Caucasians with IDDM had parietal cell antibodies. Neufield
(45) in his study found that 10% of Black Americans with IDDM

had parietal cell antibodies as compared with 8.5% in
Caucasians with IDDM.   Previous studies have
demonstrated that gastric mucosa in patients with parietal
cell antibodies is invariably abnormal with mild to severe
atrophic changes (56, 57).   Presence of parietal cell
antibodies has also been associated with achlorhydria.
Riley (52) has observed that 54% of patients with IDDM and
parietal cell antibodies had achlorhydria and 9% of patients
with IDDM and parietal cell antibodies had overt pernicious
anaemia.   Though we did not study gastric mucosa and gastric
acidity, it is suggested that IDDM patients with parietal
cell antibodies should be followed up regularly and be
screened for atrophic gastritis and achlorhydria.

ISLET CELL ANTIBODIES :   The prevalence of islet cell anti-
bodies in this study within the first one year of onset of the
disease was 5.8% and the overall prevalence of islet cell
antibodies was 3.7%.   The prevalence of islet cell antibodies
in this study is much lower than reported elsewhere (24, 25)
(Table 5).   Lendrum (24) in his study of IDDM found a strong
association between IDDM and islet cell antibodies, the
prevalence of islet cell antibodies within the first three
months of onset of IDDM was 60 - 80%, and at the end of two
years, the prevalence of islet cell antibodies was 10 - 20%.
Irvine (25) in his study of IDDM found that 56% of patients
with IDDM but without evidence of other autoimmune disease
had islet cell antibodies within the first year of onset of
IDDM.   Irvine (25) also demonstrated that 22% of patients with

IDDM but without evidence of other autoimmune disease have islet cell antibodies irrespective of the duration of IDDM. The prevalence of islet cell antibodies in patients with IDDM and with another autoimmune disease was 38%   Del Prete (58) in his study found that the overall prevalence of islet cell antibodies in patients with IDDM was 24.2%.   The prevalence of islet cell antibodies was highest within the first year of the onset of the disease and prevalence of islet cell antibodies decreased as duration of IDDM increased.

. . . .

A lower prevalence of islet cell antibodies has been noted in
U.S. Blacks with IDDM as compared with U.S. Caucasians with
IDDM (45) Neufield (45) found that 22% of Black Americans
with IDDM has islet cell antibodies as compared with 36% in
Caucasians with IDDM. Furthermore, islet cell antibodies
were present in 74% of Caucasians with IDDM within the first
three months of the onset of the disease as compared with
33% in Black Americans with IDDM within the first three
months of onset of IDDM. Our study confirms that the
prevalence of islet cell antibodies in Kenyan Africans with
IDDM is much lower when compared with Caucasian populations
and Black Americans with IDDM even though a similar assay
was used in detecting islet cell antibodies in this study.
Islet cell antibodies as detected by indirect immuno-
fluorescent assay descibred by Bottazzo (22) are found in
less than 0.5% of normal population and non diabetic
hospital controls (29). Diabetics who do not have islet
cell antibodies do not develop islet cell antibodies at a
later date (28, 59). However, patients with NIDDM or
normal subjects with islet cell antibodies will progress
given time to IDDM (28, 60). Thus islet cell antibodies
have a very high prevalence in newly diagnosed clinically
overt disease and a very low but significant prevalence in
a large control population (28). Islet cell antibodies
have also been detected using Bouin's fixed human pancreas
(61). However, it is not yet established whether these
two methods of estimating islet cell antibodies are comparable
(62). Islet cell surface antibodies detected using indirect
immunofluorescence test with dispersed islet cells from rats
are different from cytoplasmic islet cell antibodies with

different specificities and different prevalence among the
patients studied (63, 64).

Though islet cell antibodies are found in high prevalence in
newly diagnosed Caucasians with IDDM, their role in the
pathogenesis of IDDM is undefined. Islet cell antibodies
react with all the endocrine cells of islets of Langerhans.
However, it is only the beta cells which are selectively
destroyed in IDDM. Cross sectional studies suggest that there
is no obvious relationship between islet cell antibodies and
pancreatic cell function (65, 66). As has been suggested by
Irvine (19), the primary insult to the beta cells must be in
relation to the cell membrane of B cells with release of
cytoplasmic antigens, this would make islet cell antibodies
a secondary phenomenon to the processes which initially
initiated injury to the beta cells. Del Prete (58) has also
suggested that islet cell antibodies have no direct pathogenic
role in diabetes and represent a marker of other immune or
autoimmune mechanism which induce beta cell damage.

A low prevalence of islet cell antibodies in this study may
be due to a delay in seeking medical attention as is common
here which would lead to the disappearance of islet cell
antibodies as islet cell antibodies in contrast to other
antibodies are transient and tend to disappear with the
duration of the disease (24).   However, in 10 - 15% of
patients with IDDM, islet cell antibodies tend to persist
for several years after the onset of IDDM. These patients
with persistent islet cell antibodies show a female
predominance, increased prevalence of other organ specific

autoantibodies without biochemical evidence of other endocrine
disease and a later age of onset (17). These patients are
thought to have "primary" autoimmune diabetes mellitus (67).
Several studies have shown that patients with persistent
islet cell antibodies have increased incidence of HLA B8
(25, 17). As it has been mentioned before, HLA B8 occurs in increased
frequency in Caucasian diabetics due to linkage disequilibrium
with HLA DR3. Studies from various African populations with
IDDM have shown that HLA B8 occurs in reduced frequency when
compared with Caucasian populations with IDDM (68, 69). A
reduced frequency of HLA B8 has also been noted in U.S. Blacks
with IDDM (15). Though HLA antigens were not studied, it may
be that HLA B8 occurs at a reduced frequency in Kenyan Africans
with IDDM as noted in other African populations with IDDM.

Definitive clinical evidence of viral infection preceding
the onset of diabetes could only be found in a three year
old boy who developed diabetic ketoacidosis one week after
mumps. The other siblings in the family who also had
mumps at the same time did not develop diabetes, however islet
cell antibodies were not found present in this case. Islet
cell antibodies have been found in virus-induced diabetes
due to mumps, Epstein Barr virus and Coxsackie B4 virus
(39, 70). Though definitive evidence of viral infection
could only be found in one case in this study, it is possible
that many of the patients had viral infections preceding
the onset of IDDM, which may have been treated as malaria
as it is common practice here to treat any febrile illness
as malaria. A study is in progress to look into the role of
Coxsackie B4 virus in the pathogenesis of IDDM in Kenyan
Africans.

The low prevalence of islet cell antibodies and other organ
specific autoantibodies in this study suggest that "primary"
autoimmunity is not a significant factor in aetiology of
IDDM in Kenyan Africans. The other important aetiological
factors suggested in pathogenesis of IDDM include viruses
and toxins which lead to B cell destruction in genetically
susceptible individuals (71).   The precise mechanism by
which viruses and toxins lead to beta cell damage are not
well defined. However, Reeves (72) has suggested a model
whereby viruses and toxins in genetically susceptible
individuals initiate B cell destruction through cytotoxic
antibodies and/or T cells.

However, proof of viral aetiology in our study is lacking
as viral neutralizing antibodies and HLA types were not
studied.   Further studies in Kenyan Africans with IDDM
are needed to study the role of HLA antigens and the
susceptibility to develop insulin dependent diabetes
mellitus.

C O N C L U S I O N S

The data presented in this study has suggested the following :-

1.   Prevalence of islet cell antibodies in Kenyan
      Africans with IDDM is much lower than reported
      elsewhere.

2.   Prevalence of thyroid microsomal, thyroglobulin
      and parietal cell antibodies is much lower than
      reported elsewhere.

3.   Unlike the Caucasian cases of IDDM where
      concurrence of thyroid autoantibodies, which
      are indicators of autoimmune thyroiditis, occur
      in 20% of IDDM cases, it is observed in only 0.7%
      of Kenyan Africans with IDDM confirming that the
      genetic susceptibility to these diseases differs
      in two races.

4.   In view of the low prevalence of autoantibodies,
      primary autoimmune diabetes is considered rare in
      Kenyan Africans with IDDM.

5.   Islet cell antibodies are rare in non diabetic
      hospital controls.

R E C O M M E N D A T I O N S

From the study, several reommendations can be made :-

1.   Long term prospective studies are needed to
        evaluate the prevalence of IDDM in first
        degree relatives of IDDM probands.

2.   Further family and epidemiological studies are
        necessary to evaluate the role of islet cell
        antibodies as an early marker of IDDM in Kenya.

3.   HLA studies are needed to determine the genetic
        susceptibility to IDDM in Kenya.

4.   Viral studies are needed in newly diagnosed cases
        of IDDM to determine the role of viruses in
        initiating beta cell damage.

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APPENDIX A

AUTOIMMUNE PROFILES IN IDDM

NAME _____   UNIT _____

AGE _____   DATE _____

SEX _____

Date of onset of IDDM   _____.

Insulin Requirements   _____.

Clinical presentation at onset of disease _____

_____.

Episode of ketoacidosis   _____.

Diet _____.

Alcohol   Type _____   OTHER MEDICAL :

            Amount _____

            Duration _____

Family history   Parents   _____

                              _____

                    Children _____

                              _____

_____

LABORATORY DATA

BLOOD SUGAR   _____   _____   _____.

IMMUNOLOGICAL DATA

        TMA   TGA   PCA   ANA   AMA   ISAB