DECLARATION

I hereby declare that the whole thesis, unless specifically indicated to the contrary in the text, is my own original work and has not been submitted for a degree at any other university.

AYESHA AHMED MOTALA

1990

IMPAIRED GLUCOSE TOLERANCE (IGT):
A STUDY IN SOUTH AFRICAN INDIANS
IN DURBAN

SUBMITTED IN PARTIAL FULFILMENT OF
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THE STATISTICAL ANALYSES HAVE BEEN

DONE IN CONSULTATION WITH THE

INSTITUTE FOR BIOSTATISTICS OF THE

MEDICAL RESEARCH COUNCIL

For Natasha

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CHAPTER 1

INTRODUCTION

The introduction of the category of "Impaired Glucose Tolerance" (IGT) by the National Diabetes Data Group (1979), and its subsequent adoption by the World Health Organisation (WHO) Expert Committee on Diabetes (1980, 1985), was based on the observation that there are a substantial number of individuals who have a fasting plasma glucose concentration lower than that required for the diagnosis of diabetes mellitus, but in whom the plasma glucose response during an Oral Glucose Tolerance Test (OGTT) is intermediate between normal and diabetic levels.

Prior to this, substantial differences existed in the diagnostic criteria employed by diabetologists, and there was no censensus as to the dividing line between normal and diabetic glucose levels, with respect to the fasting plasma glucose concentration or its response to an oral glucose load (OGTT).

With the growth of knowledge regarding the aetiology and pathogenesis of diabetes mellitus, it was recognised that there was a need for a revision of the nomenclature, diagnostic criteria and classification of diabetes mellitus.

Owing to the lack of uniformity or standardisation in defining diabetes and other stages of glucose intolerance, problems arose in comparing data from different centres, in assessing the impact of diabetes and its complications, and in determining the epidemiology of the different categories of the disease.

Interpretation of plasma glucose levels in the fasting state and during OGTT had been based on a variety of criteria: West (1978) listed at least seventeen sets of criteria for interpreting the OGTT; of these, the four commonly employed were the criteria of the US Public Health Service (USPHS) (Remein and Wilkerson 1961), British Diabetic Association (1964), Fajans and Conn (1959, 1965) and the WHO (1965). However, a major problem was that tests deemed abnormal by one set of criteria could be classified normal by another, resulting in widely varying estimates of the prevalence of diabetes mellitus (Kobberling and Creutzfeldt 1970).

To this end, an international workshop was convened in 1978, by the National Diabetes Data Group (1979), which proposed recommendations for the classification and Diagnosis of Diabetes Mellitus and other categories of Glucose Intolerance; this was subsequently adopted with minor modifications by the WHO Expert Committee on Diabetes Mellitus as the revised WHO criteria (1980, 1985).

The decision to adopt the category of Impaired Glucose Tolerance (Jarrett et al 1979, NDDG 1979, WHO 1980) resulted from several long term observations in the UK and United States (to be quoted below) on groups of adults, whose initial glucose intolerance was of a degree of severity hitherto loosely termed chemical, latent, subclinical or asymptomatic diabetes, but again, not based on any uniformly defined criteria. It was therefore decided that individuals with plasma glucose levels intermediate between normal and diabetic be categorised as having impaired glucose tolerance, and that the previous terminologies be abandoned, since the use of the term diabetes invoked social, psychologic and economic stigmata that were unjustified in the light of the lack of severity of this category of glucose intolerance.

The significance of IGT lies in the fact that while individuals with this condition are not considered to be diabetic, prospective studies, albeit a few, have highlighted the following risks associated with IGT: 1) Progression to non insulin dependent diabetes mellitus (NIDDM) (King et al 1984; Kadowaki et al 1984; Jarrett et al 1982; Keen et al 1982; Birmingham Diabetes Survey Working Party 1976; Sazaki et al 1982; Jarrett et al 1979; O'Sullivan and Mahan 1968; Saad et al 1988). 2) Increased risk for developing macrovascular disease (Fuller et al 1980; Jarrett and Keen 1976; Jarrett et al 1982). 3) Of particular interest, however, is the paucity of microvascular complications such as retinopathy and nephropathy in subjects with IGT (Jarrett and Keen 1976; Jarrett et al 1979; Bennett et al 1976, Zimmet 1984; National Diabetes Data Group 1979).

As regards the risk of progression to diabetes mellitus, prospective studies have demonstrated that subjects with IGT may follow one of three courses: 1) Persistence of IGT; 2) Reversion to normal glucose tolerance; or 3) Progression (worsening) to non-insulin-dependent diabetes mellitus (NIDDM). From the reported studies quoted above, the proportion of individuals with IGT who progress to NIDDM over a ten-year period varies from 13% - 52%, with a rate of progression of 1% - 5% per year (National Diabetes Data Group 1979).

Of all the factors studied to date, the single most important predictor for the subsequent development of NIDDM is the plasma glucose level at the initial OGTT (either fasting or two-hour values), while the role of other factors viz. age, insulin response to a glucose load, and body mass index (BMI) remain controversial. More recently, in a study on the natural history of IGT in Pima Indians, a population with the highest incidence of NIDDM (Saad et al 1988), the best predictors of progression to NIDDM, in addition to the plasma glucose levels, were plasma insulin levels (higher fasting insulin levels and lower levels after glucose loading) and age (up to the age of 40 years, after which increasing age had a beneficial effect).

As regards IGT and macrovascular disease (atherosclerosis), some long-term studies have demonstrated an increased frequency of morbidity and mortality from macrovascular disease, especially coronary heart disease (CHD). The Whitehall Study (Fuller et al 1980) demonstrated that significant predictive risk factors for CHD mortality in subjects with IGT include systolic blood pressure, resting ECG abnormalities and age; other factors include BMI, glucose, insulin and high-density lipoprotein (HDL) - cholestrol levels. In the Bedford survey (Jarrett et al 1982) the risk for CHD mortality was found to be increased in subjects with IGT, and was greater in females.

Thus, whilst IGT individuals are NOT considered to be diabetic, they are nevertheless at a higher risk than the general population, for subsequent progression to NIDDM as well as to macrovascular disease. Hence, the presence of this entity in otherwise healthy and ambulatory individuals, may have prognostic implications and should therefore not be ignored.

The argument for detection of IGT would appear to rest on the ability to institute prophylactic measures against progression to NIDDM or to detect diabetes mellitus early after its development and so possibly prevent diabetic vascular complications by therapy.

However, evidence from the few prospective studies done to date show conflicting results in terms of any beneficial effect that therapy in such patients may have in the subsequent progression to NIDDM. (Keen et al 1982; Jarrett et al 1979; Sartor et al 1980) or the development of macrovascular disease (Jarrett et al 1977).

As regards the effect that treatment has on IGT worsening to diabetes, only three studies, using oral hypoglycaemic agents, have thus far been reported (Keen et al 1982; Jarrett et al 1979; Sartor et al 1980). However, all these studies have shortcomings in terms of sample size. Moreover, there was a significant cohort drop out rate in the Swedish Study (Sartor et al 1980). Notwithstanding the shortcomings, the last study showed that while none of the twenty three subjects who continued on a regimen of dietary restriction and tolbutamide progressed to diabetes mellitus over a ten-year period, 29% of those on no treatment progressed to diabetes mellitus. In contrast, the two British studies, the Whitehall Survey (Jarrett et al 1979) and the Bedford survey (Keen et al 1982), demonstrated that worsening to diabetes was not significantly influenced by treatment, which included carbohydrate restriction combined with phenformin (Whitehall Survey) or tolbutamide (Bedford Survey), or carbohydrate restriction alone.

On the basis of these studies, a number of possible strategies may be implemented regarding the approach to management of subjects with IGT (Bennett 1985, Zimmet 1982): these include 1) observation without treatment but with follow up OGTT. 2) weight reduction by kilojoule restriction and exercise. 3) management of risk factors for CHD viz. Hypertension, and 4) drug therapy.

The lack of uniformity in decisions on management is largely due to the fact that there have been surprisingly few studies done to determine the effects of intervention on IGT. As has been highlighted (Bennett 1985), there is a need for further population-based studies, since if intervention could successfully alter the natural history of IGT, it would be a major public health achievement, which could lead to a reduction in the incidence of diabetes mellitus and perhaps also CHD.

However, before interventional studies are undertaken, it is vital that prospective population-based studies be performed to determine the significance of IGT with respect to its mechanisms and prognostic implications in different populations.

It is therefore not surprising, that there has been a call from the WHO Expert Committee on Diabetes (1980, 1985) for further population-based studies of IGT, in an attempt to shed light on the validity of this entity (as well as to provide evidence concerning the present diagnostic criteria for glucose tolerance).

Moreover, prospective studies of subjects with this entity may provide clues as to the aetiology and pathogenesis of diabetes mellitus.

To date, there have been no documented studies on IGT in any of the various population groups in South Africa. In fact, even elsewhere, the only non-caucasoid groups studied have been the Pima Indians, the Nauruans and the Japanese.

South African Indians, a migrant Indian group, have a high prevalence of diabetes mellitus (Omar et al 1985). Therefore it would be of paramount importance to provide demographic data on IGT in this population group. All that is known is that the prevalence of IGT is 5.8%; its significance however, remains to be determined.

In the light of the foregoing information, this prospective study was undertaken to examine the various clinical and biochemical parameters in a group of South African Indian subjects with IGT. It is hoped that such a study will bring to light any distinctive features that may have a bearing on the pathogenesis and natural history of IGT in this population.

CHAPTER 2

MATERIALS AND METHODS

POPULATION STUDIED:

A total number of 128 Indian subjects with IGT (61 females and 67 males) were recruited as part of a prospective study, between 1985 and 1988.

The subjects studied, were all drawn from a group which was diagnosed as having IGT in 1984 in an epidemiological survey which was aimed at determining the prevalence of Diabetes Mellitus among South African Indians living in the city of Durban, and which was conducted by systematic cluster sampling of households. All adults over the age of 15 years were studied. The study was based on a modified oral glucose tolerance test (OGTT) using the revised WHO criteria.

Of the 2479 subjects studied in 1984, 5.8% (143 subjects) had IGT (Omar et al 1985 and unpublished data). Of these 143 subjects, 128 consented to participate in a proposed prospective study.

The Indian patients studied were descendants of migrants who had immigrated to South Africa from the Indian sub-continent, in the latter half of the 19th century. They comprise two ethnic subgroups viz: the Aryans and the Dravidians, whose predecessors originated from North and South India respectively (Mistry 1965).

All chosen subjects were interviewed by a social worker prior to the day of the test, and where consent was obtained, the tests were conducted at a central point, either a clinic or a hospital. In view of this being a community and not a hospital based study, several interviews were often necessary, before a positive response was achieved.

METHODS:

The patients studied had the following data recorded:

(A) HISTORY:

1. Age, Sex
2. History of diabetes mellitus
   Hypertension
   Ischaemic Heart Disease
   Smoking
3. Family history of diabetes mellitus

(B) CLINICAL EXAMINATION INCLUDED:

1. Weight, Height, Body Mass Index (BMI).
2. Blood pressure
3. Presence or absence of peripheral pulses
4. Opthalmological examination for cataracts or evidence of retinopathy.

BODY MASS INDEX (BMI)

Height and weight were measured in order to determine Body Mass Index (BMI), based on the following formula:

$$\frac{\text{Weight (Kg)}}{\text{Height (m)}^2}$$

Obesity was defined as a BMI $\geq$ 25 for females.
$\geq$ 27 for males

BLOOD PRESSURE:

Consecutive duplicate readings recorded to the nearest 2mm were performed on the subjects in a rested position, using standard mercury sphygmomanometers. Systolic blood pressure was recorded at the level of appearance of sound, and diastolic blood pressure at the level of its disappearance (phase V). If measurements were unacceptably discrepant, a third reading was taken. The means of the two closest sets of readings were used for purposes of analysis.

Hypertension was classified based on WHO recommendations (WHO 1978) i.e. systolic blood ≥ 160 mmHg and / or diastolic blood pressure ≥ 95 mmHg.

RETINOPATHY:

Fundal examination was performed without prior installation of a mydriatic agent.

Diabetic Retinopathy was classified as background if there were microaneurysms, exudates or small haemorrhages; or as proliferatiive if there were large haemorrhages, neovascularisation, retinal or vitreous fibrosis or retinal detachment.

Where present, evidence of hypertensive retinopathy was also recorded.

(C) INVESTIGATIONS

1. 75 G Oral Glucose Tolerance Test (OGTT)
2. Insulin Response to Oral Glucose Load (during OGTT)

   Insulinogenic Index $\frac{\Delta \text{ Insulin}}{\Delta \text{ Glucose}}$
3. Fasting Serum Total cholesterol

   Serum Total Triglyceride

   Serum HDL cholesterol

4. Serum Uric Acid
5. Glycosylated Haemoglobin (GHb)
6. Resting Electrocardiograph (ECG)
7. In a subset of patients :
   - Stress Test - Bruce Protocol
   - HLA Studies.

ORAL GLUCOSE TOLERANCE TEST (OGTT)

A two-hour OGTT was performed after an overnight fast of 10-12 hours. Subjects were on unrestricted diets prior to the test (since restriction to less than 125g of CHO may affect glucose tolerance). Smoking was not permitted for the duration of the fast and the test.

A butterfly - 21 Int. Winged Needle Infusion set was introduced into a forearm vein under local analgesia, and kept patent with 0.9% saline infusions.

Fasting (basal) venous blood samples for plasma glucose and insulin were taken after a rest period of at least 30 minutes. Following collection of basal samples, the subject was instructed to drink within five minutes, 75g (416 mmol) of glucose monohydrate dissolved in 250ml of water. After the first sip, timed blood samples were withdrawn at 15 minute intervals, for the first half hour, and thereafter, at 30 minute intervals, for the next 90 minutes.

Blood samples were collected in tubes containing sodium fluoride and in plain tubes (for the determination of plasma glucose and insulin levels respectively); the blood samples were immediately centrifuged and the plasma separated and stored at - 30°C.

Plasma glucose concentration was measured by means of an Autoanalyser employing the glucose oxidase method (Beckman Autoanalyser), and Plasma Insulin was determined by Radio immunoassay, using the double antibody technique (Phadeseph Kits).

BASAL (FASTING) LIPID PROFILES, SERUM URIC ACID, GLYCOSYLATED HAEMOGLOBIN

Fasting blood samples for Serum Total Cholesterol and Triglyceride and High Density Lipoprotein (HDL) - cholesterol were collected into plain tubes.

Total serum cholesterol concentrations were determined by an enzymatic colorimetric method (Monotest(R) Cholesterol, Boehringer Mannheim GmbH Diagnostica). Total serum triglyceride concentrations were determined by an enzymatic colorimetric method (Periodochrom(R) Triglyceride GPO-PAP, Boehringer Mannheim GmbH Diagnostica). Serum HDL-cholesterol concentrations were determined by a precipitation procedure (Monotest(R) cholesterol and HDL-Cholesterol Precipitant, Boehringer Mannheim GmbH Diagnostica).

Fasting venous blood samples were collected into EDTA containing blood tubes, for the determination of Haemoglobin A_1, (HbA_1), a glycosylated haemoglobin.

HbA_1 ($HbA_{1(a+b+c)}$) was measured using the Helena GLYCO Hb QUICK COLUMN PROCEDURE, which is a cation - exchange microchromatographic method for the quantitation of HbA_1.

Venous blood samples were drawn into plain tubes, for measurement of plasma uric acid concentration which was determined by an enzymatic colorimetric method (Periodochrom$^{(R)}$ Uric Acid, Boehringer Mannheim GmbH Diagnostica).

The interassay C.V. for the various biochemical analyses was as follows:

Total cholesterol	: 1.5 - 2%
Total triglyceride	: 1.5 - 3%
Uric acid	: 2.4%
HbA_1	: 2.7%
Insulin	: < 5%

ELECTROCARDIOGRAM (ECG) AND EXERCISE STRESS TEST (EST)

A resting 12 - lead ECG was performed and was reported using the Minnesota Code.

A subset of the study group had treadmill exercise stress tests (EST). Patients were exercised on the Quinton 2000 stress system, using the graded multi-stage Bruce Protocol. Three standard electrocardiographic leads - V1, avf and V5 - were continuously monitored by a three-channel oscilloscope. ST-segment was measured 80 m sec from the J-point.

Exercise was continued for three minutes at each stage. Patients were encouraged to exercise to their maximum. Tests were terminated if the patient developed symptoms of chest pain, fatigue, dyspnoea, claudication, arrhythmia, or if marked ST-segment changes developed on the electrocardiogram.

HLA STUDIES

HLA A, B, C, and DR specificities were done on a subset of the patients. A two-stage lymphocytotoxicity test using 180 antisera was employed to determine HLA A, B, C and DR antigens. An extended incubation microlymphotoxicity test using B cell-enriched, T cell-depleted lymphocytes was employed to determine HLA DR antigens.

STATISTICAL ANALYSIS

Statistical analyses were performed with programs of the SAS (Statistical Analysis System) Institute (1988). Where comparisons between several groups was required; this was performed by analysis of variance (ANOVA) (GLM [general linear model] program) or the chi-square method. Duncan's multiple range test was employed to evaluate the difference between any two groups of the four (or three) groups analysed by analysis of variance.

Statistical correlations were obtained by Pearson's simple correlation coefficient (r) and the regression lines calculated by the least squares method. The comparison of the slopes of the regression lines was obtained by student's t test for differences between regression slopes.

For the multivariate analysis, to evaluate the effect of various risk factors, the multiple logistic regression model was used to predict progression to diabetes. Selection of variables was done in a stepwise fashion with the use of a **backward elimination method** (Armitage P and Berry G 1987).

FOLLOW-UP EXAMINATION

The OGTT was performed on all subjects at year 1. The subjects were then divided into three groups, according to the results of the OGTT at year 1:

IGT - the group which *persisted* with IGT

Diabetic - the group which *progressed* to NIDDM

Normal - the group which *reverted* to NORMAL glucose tolerance

Further follow-up was determined according to the group to which the subjects belonged. Thus all those who persisted with IGT or reverted to Normal, were asked to undergo an OGTT at year 4. In addition, a subgroup of those who persisted with IGT or reverted to Normal, had follow-up OGTT at year 2.

The end point of study for any subject was the date of diagnosis of NIDDM.

CONTROL SUBJECTS:

The control subjects consisted of healthy employees or relatives of employees from various departments at the University of Natal. They were not known to have diabetes or any other medical disorder. Informed consent was obtained from all participants.

CLASSIFICATION AND DIAGNOSIS

Diagnosis of IGT and Diabetes Mellitus was based on the revised WHO criteria (1985), recommended by the World Health Organisation Expert Committee on Diabetes. These criteria are based on a two hour oral glucose tolerance test using a 75g oral glucose load (as described earlier in this chapter). Table 1 outlines the diagnostic criteria employed (from WHO Tech Rep Ser 1985).

Table 1

DIAGNOSTIC VALUES FOR ORAL GLUCOSE TOLERANCE TEST UNDER STANDARDS CONDITIONS. LOAD 75g GLUCOSE IN 250-350ml OF WATER FOR ADULTS OR 1.75g/Kg BODY WEIGHT (TO A MAXIMUM of 75g) FOR CHILDREN, USING SPECIFIC ENZYMATIC GLUCOSE ASSAY.

	GLUCOSE CONCENTRATION mmol/litre (mg/dl)			
	WHOLE BLOOD		PLASMA	
	Venous	Capillary	Venous	Capillary
Diabetes Mellitus				
Fasting Value				
	≥6.7	≥6.7	≥7.8	≥7.8
	(≥120)	(≥120)	(≥140)	(≥140)
2 Hours After Glucose Load				
	≥10.0	≥11.1	≥11.1	≥12.2
	(≥180)	(≥200)	(≥200)	(≥220)
Impaired Glucose Tolerance				
Fasting Value				
	<6.7	<6.7	<7.8	<7.8
	(<120)	(<120)	(<140)	(<140)
2 Hours After Glucose Load				
	6.7-10.0	7.8-11.1	7.8-11.1	8.9-12.2
	(120-180)	(140-200)	(140-200)	(160-220)

CHAPTER 3A

CLINICAL FEATURES OF THE STUDY GROUP

INTRODUCTION

The category of Impaired Glucose Tolerance (IGT) as a distinct entity has only relatively recently been introduced by the National Diabetes Data Group (1979). It was subsequently adopted by the WHO Expert Committee on Diabetes (1980, 1985).

The significance of IGT lies in the fact that a few long term studies have highlighted an increased risk for subsequent progression to NIDDM (King et al 1984; Kadowaki et al 1984; Jarrett et al 1982; Keen et al 1982; Birmingham Diabetes Survey Working Party 1976; Sazaki et al 1982; Jarrett et al 1979; O'Sullivan and Mahan 1968; Saad et al 1988) and development of macrovascular disease (Fuller et al 1980; Jarrett and Keen 1976; Jarrett et al 1982).

To date, there have been no documented studies on IGT in any of the various population groups in South Africa. South African Indians have a high prevalence of diabetes (Omar et al 1985), and it would therefore be important to provide data on IGT in this population group. All that is known is that the prevalence of IGT is 5.8% (Omar et al 1985); its significance, however, remains to be determined.

PATIENTS AND METHODS

128 South African Indians living in the city of Durban consented to participate in this study. They were recruited from the 143 subjects who fulfilled the criteria for diagnosis of IGT in an epidemiological survey in 1984 (Omar et al 1985, and unpublished data).

The following data were recorded from all the patients studied:

(A) HISTORY

1. Age, Sex
2. History of diabetes mellitus, hypertension, ischaemic heart disease, smoking, alcohol intake.
3. Family history of diabetes mellitus in a first degree relative (defined as mother, father, sibling or offspring).

(B) CLINICAL EXAMINATION

1. Weight, height and Body Mass Index (BMI) which was calculated thus : $\frac{\text{Weight (Kg)}}{\text{Height (m)}^2}$
2. Blood pressure
3. Presence or absence of peripheral pulses
4. Opthalmological examination for cataracts and evidence of retinopathy (as described in Chapter 2).

RESULTS AT YEAR 1

Results are shown in Table 1 - 4 and Figure 1 and 2.

SEX AND AGE: **Table 1 - 3; Figure I**

67 males and 61 females were studied. The mean age was 48.5 ± 1.1 years (20-80 years). In males, the mean age was 48.5 ± 1.5 (22-77 years) and in females 48.4 ± 1.6 (20-80 years).

Figure I illustrates the age distribution of the subjects studied. 88.3% (113 subjects) were over 35 years, with an increased prevalence (83.6%) between 35-69 years; only 6 subjects (4.7%) were over 70 years, and 8 subjects (6.3%) under 35 years. 93.8% (120 subjects) were over 30 years. The age distribution was similar in both sexes.

FAMILY HISTORY

Details of family history are shown in Table 1.
A positive history of diabetes affecting a first degree relative was obtained in 69 subjects (53.9%). A history of maternal diabetes (34.4%) was commoner than that of paternal diabetes (15.6%).

As regards siblings, a history of diabetes amongst brothers and sisters was obtained in 27 subjects (21.1%) and 21 subjects (16.4%) respectively.

TABLE 1

CLINICAL CHARACTERISTICS OF THE STUDY GROUP

AT YEAR 1 - HISTORICAL INFORMATION

NUMBER OF PATIENTS	128	
MALE:FEMALE RATIO	67:61	
*AGE (YEARS)	48.5±1.1 (20-80)	
PERSONAL HISTORY:		
DIABETES MELLITUS	0	
HYPERTENSION	14	
ISCHAEMIC HEART DISEASE	6	
SMOKING	42	
ALCOHOL	4	
	n	%
FAMILY HISTORY OF DIABETES:	69	53.9
Father	20	15.6
Mother	44	34.4
Brother	27	21.1
Sister	21	16.4
Son	2	1.6
Daughter	0	0.0

*MEAN ± S.E. (RANGE)

TABLE 2

CLINICAL CHARACTERISTICS OF THE STUDY

GROUP AT YEAR 1 - CLINICAL EXAMINATION

	TOTAL	MALES	FEMALES	P
*NUMBER	128	67	61	
*AGE (YEARS)	48.5±1.1(20-80)	48.5±1.5(22-77)	48.4±1.6(20-80	ns
*WEIGHT (Kg)	66.5±1.1(40-106.5)	69.2±1.4(45-97)	63.6±1.6(40.2-106.5)	
*HEIGHT (cm)	160.6±0.8(140-180)	166.8±0.6(156-180)	153.8±1.0(140-180)	
*BMI	25.8±0.4(16.8-40.7)	24.8±0.5(16.8-35.3)	26.95±0.6(16.96-40.7)	0.008
OBESITY n(%)	54 (42.2)	18 (26.9)	36 (59)	
*BLOOD PRESSURE (mmHg)				
SYSTOLIC	129.9±1.8 (90-190)	128.8±2.3 (100-190)	131.2±2.8 (90-190)	ns
DIASTOLIC	81.4±1.2 (50-120)	81.4±1.6 (60-120)	81.4±1.8 (50-120)	ns
HYPERTENSION n(%)	22 (17.2)	10 (14.9)	12 (19.7)	
PERIPHERAL VASCULAR DISEASE	0	0	0	
OPTHALMOSCOPY (n)				
CATARACTS	7	3	4	
RETINOPATHY				
DIABETIC	0	0	0	
HYPERTENSIVE	6	4	2	

*MEAN ± S.E. (RANGE)

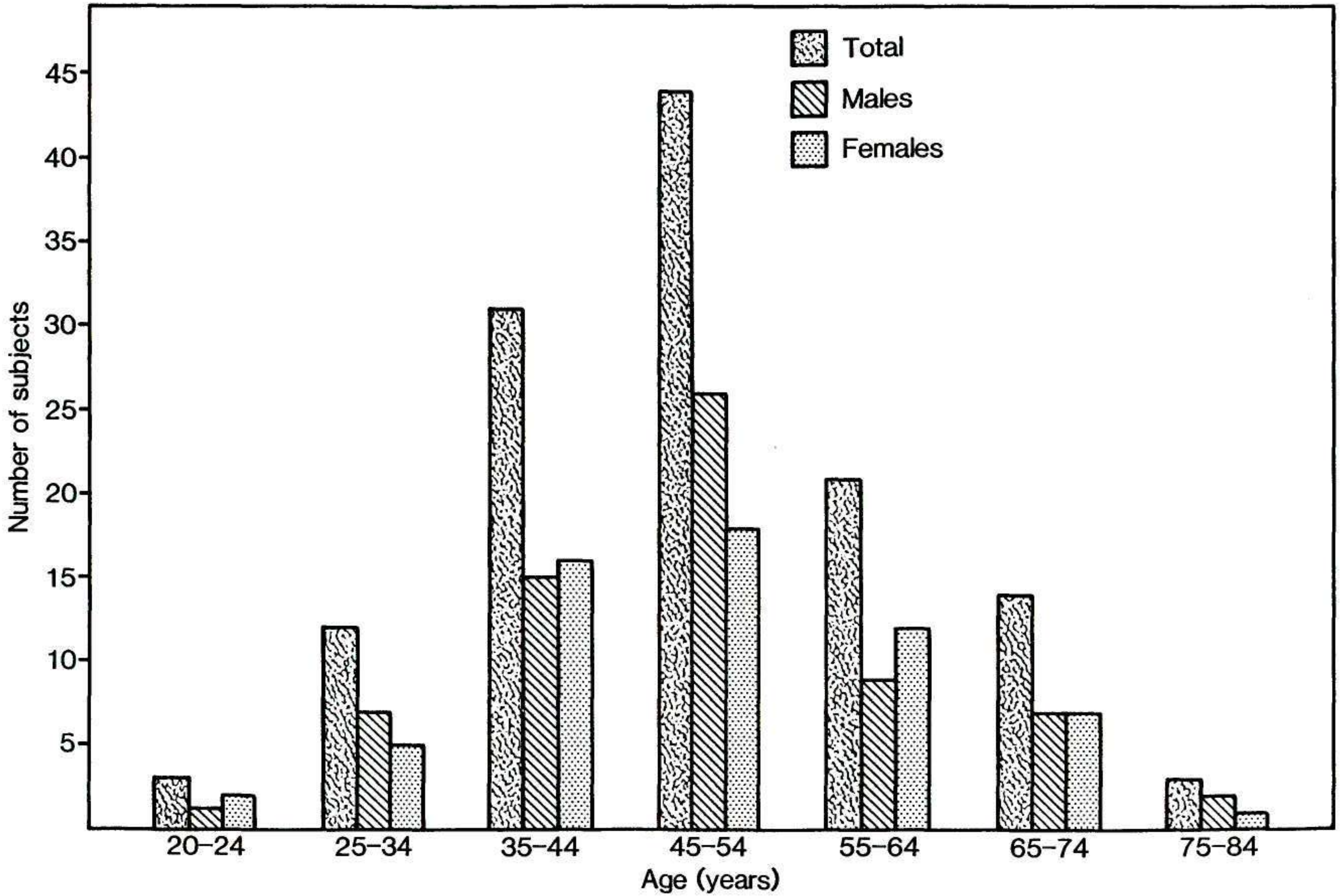


Figure 1: Age distribution in the study group.

TABLE 3

AGE DISTRIBUTION

AGE GROUP (YEARS)	TOTAL		MALE		FEMALE	
	n	%	n	%	n	%
20 - 24	3	2.3	1	1.5	2	3.3
25 - 34	12	9.4	7	10.5	5	8.2
35 - 44	31	24.2	15	22.4	16	26.2
45 - 54	44	34.4	26	38.8	18	29.5
55 - 64	21	16.4	9	13.4	12	19.7
65 - 74	14	10.9	7	10.5	7	11.5
75 - 84	3	2.3	2	3.0	1	1.6
TOTAL	128	100	67	100	61	100

TABLE 3

AGE DISTRIBUTION

AGE GROUP (YEARS)	TOTAL		MALE		FEMALE	
	n	%	n	%	n	%
20 - 24	3	2.3	1	1.5	2	3.3
25 - 29	5	3.9	2	3.0	3	4.9
30 - 34	7	5.5	5	7.5	2	3.3
35 - 39	17	13.3	10	15.0	7	11.5
40 - 44	14	10.9	5	7.5	9	14.8
45 - 49	27	21.1	15	22.4	12	19.7
50 - 54	17	13.3	11	16.4	6	9.8
55 - 59	15	11.7	7	10.5	8	13.1
60 - 64	6	4.7	2	3.0	4	6.6
65 - 69	11	8.6	5	7.5	6	9.8
70 - 74	3	2.3	2	3.0	1	1.6
75 - 79	2	1.6	2	3.0	0	0.0
80 - 84	1	0.8	0	0.0	1	1.6
TOTAL	128	100	67	100	61	100

Only 2 subjects (1.6%) had an offspring with diabetes.

PERSONAL HISTORY: **Table 1**

None of the subjects had diabetes mellitus previously. 14 subjects (10.9%) were known patients with Hypertension; of these, 2 subjects were on treatment with a thiazide diuretic (dyazide), whilst the other subjects were treated with a ß-adrenergic blocker (4 subjects), Methyldopa (5 subjects) or rauwolfia derivative, reserpine (2 subjects). One patient was on no therapy for hypertension.

Of the 6 subjects (4.7%) who gave a positive history of Ischaemic Heart Disease, 3 had a past history of myocardial infarction, and one such subject had undergone coronary artery by-pass surgery (latter subject admitted to angina as well). A history of angina without documented myocardial infarction, was obtained in 3 other subjects. Of the subjects with a history of IHD, 5 were being treated with ß-adrenergic blocking agent (2 of whom had hypertension as well), and 1 subject with nifedipine.

42 subjects (32.8%) were cigarette smokers and 4 subjects (3.1%) admitted to an alcoholic history.

BODY MASS INDEX (BMI) **Table 2 and 4 ; Figure 2**

The Mean BMI of the study group was 25.8 ± 0.4 (16.8 - 40.7). In females the Mean BMI was significantly higher, 26.95 ± 0.6 than in males 24.8 ± 0.5, $p = 0.008$. 54 subjects (42.2%) were classified as

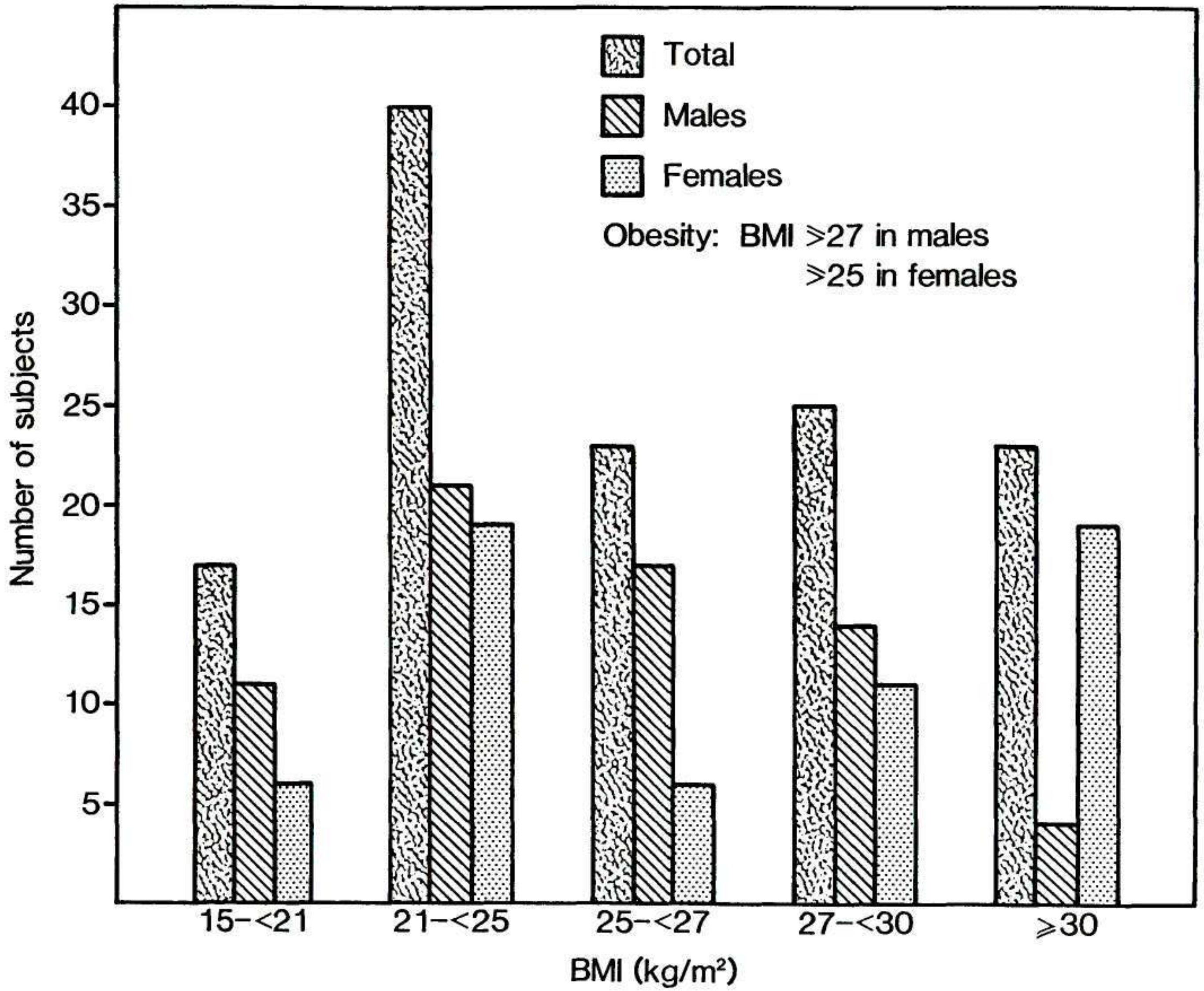


Figure 2: BMI distribution in the study group.

TABLE 4

B.M.I. DISTRIBUTION OF STUDY GROUP

B.M.I.	TOTAL		MALE		FEMALE	
	n	%	n	%	n	%
15 - < 21	17	13.3	11	16.4	6	9.8
21 - < 25	40	31.3	21	31.3	19	31.2
25 - < 27	23	18.0	17	25.4	6	9.8
27 - < 30	25	19.5	14	20.9	11	18.0
≥ 30	23	18.0	4	6.0	19	31.2
TOTAL	128	100	67	100	61	100
Obesity ≥ 27 males ≥ 25 females	54	42.2	18	26.9	36	59

DISCUSSION

Since the category of IGT has been recognised as a distinct entity for a relatively short period of time (NDDG 1979), it is hardly surprising that little information is available on its epidemiology and significance. This is further hampered by the fact that comparison of prevalence rates in different countries (and even for different populations in the same country) has been almost impossible because of different methodologies and diagnostic criteria employed.

Whilst reports on longitudinal studies of IGT, albeit a few, do exist in the literature (Saad et al 1988; King et al 1984, Kadowaki et al 1984; Jarrett et al 1982; Keen et al 1982; Sazaki et al 1982; Fuller et al 1980; Jarrett et al 1979; Jarrett and Keen 1976; Birmingham Diabetes Survey Working Party 1976; O'Sullivan and Mahan 1968), actual prevalence data for IGT using WHO criteria (1985) appear to be lacking, with the notable exception of data among various Pacific populations (Zimmet et al 1982). Table 5 attempts to list prevalence rates using the revised WHO crieria.

Studies on the two populations with the highest prevalence of NIDDM in the world viz. the American Pima Indians and the Micronesians in Nauru, provide useful models for studying the natural history of IGT. In the Micronesian population of Nauru, the prevalence of IGT was 22.4% (which is the highest in the world), the rate being slightly higher in females (25.1%) than in males (19.4%) (Zimmet et al 1977, 1982). In the Pima Indians, who have the world's highest prevalence of NIDDM - 35.1% (Bennett et al 1971; Knowler et al 1978), the prevalence of IGT was 11%, being again, higher in females (12.7%) than in males (9.4%).

The prevalence of NIDDM has been noted to be higher in Migrant Asian Indian population (Zimmet et al 1983, Omar et al 1985, Mather et al 1985) as compared to Indians living in India (WHO 1980, Rao et al 1989, Verma et al 1986), although comparison with the latter two studies in India, as well as with the Southall survey (Mather et al 1985) is difficult, because in these studies the prevalence rates were obtained by questionnaire method and not based on oral glucose tolerance testing. However, whilst some information is available on prevalence of NIDDM, no information is available on prevalence rates of IGT in Indians living in India.

The overall crude prevalence of IGT in Fijiian Indians is high, 10.5%. Using age-standardised prevalence rates these were higher in rural males (10.2%) than urban males (8.3%); whilst the rate was higher in the urban females (11.8%) compared to the rural females (9.6%). (Zimmet et al 1983).

The only data available on IGT prevalence using WHO criteria in South African Indians (Omar et al 1985), is the report on the study performed on Indians living in Durban (and from which the subjects for this these were drawn). This study reported that the overall crude prevalence of IGT was 5.8%, with a higher prevalence in males (7.6%) compared to females (4.8%).

Little information is available on the family history of abnormal glucose tolerance in subjects with IGT. The significance of family history lies in the fact that in certain populations viz. Pima Indian, Pacific Island populations and migrant Asian Indians, the high prevalence of diabetes may be due to a genetic susceptibility ('diabetic genotype') and that the disease is unmasked by environmental factors (Zimmet P 1982), consistent with the "thrifty genotype" hypothesis proposed by Neel (1962,1982).

Thus, if a genetic tendency for the development of diabetes does exist, and if IGT is a risk factor for worsening to NIDDM in any population group being studied, then perhaps family history may be an important factor to be examined.

Yet the evidence for its importance as a risk factor appears to be lacking.

In the present study, 69 subjects (53.9%) gave a positive family history of diabetes in first degree relatives. This finding is similar to that found in the Micronesian population in Nauru (Zimmet

The sex distribution in the present study was almost equal, M:F ratio 67:61. In the original study (Omar et al 1985), the prevalence of IGT was higher in males (7.8%) than females (4.8%). However, since the sample comprised more females than males, in terms of actual numbers the sex distribution was almost equal.

The Mean Age of 48.5 years, found in this study, compares with that found in Nauruan subjects with IGT (Zimmet et al 1984). The observation in the present study that 88.3% of the subjects were ≥ 35 years is higher than that found in Pima Indian (Bennet 1971) in whom 60.9% of subjects with IGT fell into this age group. In the present study, an equal sex distribution was found in subjects ≥ 35 years of age (88.1% and 88.5% of males and females respectively), as compared to the Pima Indian study, in which the rate was higher in males (78%) than in females (50%).

In the prospective study of 51 Nauruan subjects with IGT (King et al 1984), 63% were ≥ 30 years at the baseline examination, the distribution being similar in males (59%) and in females (62.7%), compared to the present study in which 93.8% of the subjects were ≥ 30 years, again with the sex distribution being similar (95.5%, 91.8% of males and females respectively). Thus, in South African Indians, IGT appears to be associated with increased age, more so than in either the Pima Indians or Nauruans.

In the present study, the Mean BMI of 25.8 is similar to that found in the original study (Omar et al 1985), in which the Mean BMI of the IGT group was 25.8 ± 6.6. This was significantly higher compared to the group with Normal Glucose Tolerance (22.1 ± 2.8.). Moreover, in the present study, the Mean BMI in females (26.95 ± 0.6) was significantly higher than in males (24.8 ± 0.5) p = 0.008. The high Mean BMI of the group as a whole, was probably contributed to by the high Mean BMI in the females.

Obesity was present in 42% of the subjects examined, and was more prevalent in females than in males; 59% of the females studied were obese, as compared to males, of whom only 26.9% were obese.

If increased BMI and obesity were a risk factor for progression to NIDDM then it would be feasible to predict that more females than males, in the present study, would progress to NIDDM. However, evidence for this from prospective studies in other population groups with IGT, is conflicting.

In prospective studies in Pima Indian (Saad et al 1988) and Nauruans (King et al 1984), BMI and obesity proved to be risk factors for subsequent progression to diabetes in univariate analyses, although in both studies, these failed to achieve significance in the multiple logistic regression model. In another report of a follow-up study of 697 Pima Indians with IGT (Knowler et al 1986) diabetes incidence was found to be positively related to initial BMI, especially in those subjects aged between 25 - 54 years.

In the Bedford Survey (Keen et al 1982), BMI was found to be an independent and significant predictor of worsening to diabetes over a 10-year period; the baseline Mean BMI in the group which worsened to NIDDM being significantly higher (29.2 ± 1.0) compared to the group which did not (26.3 ± 0.3); the presence of obesity at baseline doubling the risk of deterioration - i.e. 19-5% vs 9.3%.

However in another British study, viz: the Whitehall Survey (Jarrett et al 1979), baseline BMI did not appear to be a risk factor for worsening to NIDDM, the Mean BMI being similar in the group which worsened to diabetes (27.0 ± 3.8) compared to the group which did not (26.1 ± 3.4).

In Japanese subjects with IGT (Kadowaki et al 1984), a high maximal body weight index was a significant independent risk factor for development of diabetes over a 5 - 12 year period. In another Japanese study, in Osaka (Sazaki et al 1982), in which a 7 - year follow-up was performed on 207 subjects (161 Normal Glucose Tolerance, 13 IGT, 33 Diabetes), the rate of worsening to diabetes was higher in obese compared to non-obese subjects with IGT (15.6% vs 4.5% respectively). However, it is difficult to draw any conclusions from that particular study, in view of the small number of IGT subjects at the baseline (13 subjects).

In the light of the foregoing information it is probable that the high prevalence of obesity and increased BMI, found in the present study, has a significant role to play in the natural history of IGT in this population, particularly in females.

Apart from the risk of progression to NIDDM, subjects with IGT are at risk of macrovascular disease (atherosclerosis) (see Chapter 1), for which the major risk factors include systolic blood pressure, age and ECG abnormalities at the baseline examination. Other risk factors include BMI, blood glucose, insulin and HDL cholesterol levels. In the Whitehall survey (Fuller et al 1980) the 7½ year CHD mortality rates per 1000 in the IGT group was 65.5% in subjects with systolic blood pressure $\geq$ 153 mmHg compared to 31.3% in those in whom the systolic blood pressure was $<$ 153 mmHg. On the other hand, the Bedford Study (Jarrett et al 1982) found that although IGT was a greater risk for CHD mortality in women than men, this could not be explained by blood pressure at the baseline examination.

Whilst, in the present study, the Mean Blood Pressure of : $\frac{129.9}{81.4}$ mmHg would appear innocuous, the wide range $\frac{(90 - 190)}{(50 - 120)}$ mmHg seems to be more important

Moreover 21% of the subjects had systolic blood pressure $\geq$ 150 mmHg; thus it would be conceivable on the basis of the studies quoted above, that these subjects might be at risk of CHD with its attendant morbidity and mortality.

The high prevalence of Hypertension (9.8%) in South African Indians has been recorded previously (Seedat et al 1978). In a recent report of a community survey (Omar et al 1988), the prevalence of Hypertension in South African Indians with IGT was 31.4%, compared to 9.9% in those with Normal Glucose Tolerance, the sex distribution being similar in both groups. With respect to age, the IGT group in that study showed a significantly higher systolic and diastolic blood pressure in the 40 - 49 year age group, when compared to the group with normal glucose tolerance.

As regards BMI and coronary heart disease in IGT subjects, the Whitehall survey (Fuller et al 1980) found that obesity was associated with a higher relative risk of CHD death in the IGT group than in the normoglycaemic group; however BMI lost its significance as an independent predictor in the multiple logistic regression analysis. Therefore, in the present study it would be important to examine BMI as a risk factor for CHD, especially since a significantly high percentage of the study group (42%) were obese.

The lack of evidence for diabetic retinopathy in the present study supports the findings of most other workers (Bennett et al 1971; Jarrett and Keen 1976; Zimmet et al 1984). Cataracts were present in seven subjects and the most plausible reason is that these were senile cataracts (since all these subjects were › 65 years); the remote possibility that this might be related to IGT per se should be borne in mind.

The finding that 10.9% of the subjects were known to have hypertension is in keeping with the recent finding that South African Indian subjects with IGT have a higher prevalence of hypertension than those with Normal Glucose Tolerance (Omar et al 1988, see above).

It is well known that drugs, in particular thiazide diuretics, may impair glucose tolerance (NDDG 1979). However in this study, since only 2 subjects with hypertension were being treated with thiazide diuretic, they were not excluded from the analysis, since it was considered unlikely that this particular factor would influence results in the ultimate analysis (this point will be discussed in ensuing chapters).

That only 6 subjects (4.7%) gave a positive history of IHD was in fact surprising; firstly, because of the known association between coronary heart disease and IGT (see above), as well as the documented high prevalence of IHD (59.8%) in young South African Indians and whites (Wyndham C.H. 1982). In a study which examined abnormal glucose tolerance and lipid abnormalities in South African Indian Myocardial Infarct Survivors (Sewdarsen et al 1983), IGT was found in 14% of the subjects, and the results of that study suggested that abnormal glucose tolerance was a significant risk factor for CHD in this population group. However, since in the present study, the information on IHD was obtained by questionnaire method, the actual prevalence of this entity may be higher, and will, hopefully be more clearly elucidated, when the results of the analysis of ECG/Stress Test data are presented, later in this report.

SUMMARY

128 South African Indian subjects with IGT (67 males and 61 females) were studied with respect to their clinical characteristics. The Mean Age of the group was 48.48 years and 88.3% were ≥ 35 years. A positive family history of diabetes was found in 54% of the group, a history of maternal diabetes being commoner (34.4%) than that of paternal diabetes (15.6%). In females, the Mean BMI was significantly higher (26.95 ± 0.6) than in males (24.8 ± 0.4) $p = 0.008$; with 31.2% of the females having BMI ≥ 30. Obesity, which was found in 42.2% of the group, was more prevalent in females (59%) than in males (26.9%).

Twenty two subjects (17.2%) were defined as having hypertension which was present as commonly in males as in females (M:F = 10:12). None of the subjects displayed evidence of microvascular complications viz. retinopathy.

Table 5 PREVALENCE OF IMPAIRED GLUCOSE TOLERANCE (IGT) IN DIFFERENT POPULATIONS

POPULATION STUDIED	AUTHORS	NUMBER STUDIED	CRITERIA FOR IGT	MEAN OR RANGE OF AGE (YEARS)	PREVALENCE (%) OF IGT TOTAL	MALE	FEMALE
UNITED STATES:							
Pima Indians	Bennett et al 1971	2917		≥5	~11.0	~9.4	~12.7
Blacks	*Harris et al 1987, 1989	3872	WHO	20–74	12.7	11.3	13.6
Whites					10.7	10.2	11.1
Japanese Nesei Men	*Fujimoto et al 1987	153	WHO	61		39.2	
PACIFIC POPULATIONS:	Zimmet et al 1982			≥20			
Micronesians (Nauru)		456	WHO		22.4	19.4	25.1
Polynesians (New Caledonia)		401	WHO		8.0	4.9	10.1
Melanesians (New Caledonia)		535	WHO		5.0	3.5	6.2
FIJI:	Zimmet et al 1983	2638	WHO	≥20			
Melanesians						rural 6.2	rural 10.2
						urban 8.0	urban 13.8
Indians						rural 10.4	rural 10.8
						urban 9.4	urban 11.2
MAURITIUS:	Dowse et al 1990	5080	WHO	25–74			
Indians: Hindu					16.2	12.6	19.7
Muslim					15.3	11.1	19.5
Creoles					17.5	15.4	19.6
Chinese					16.4	13.6	19.3
SOUTH AFRICA:							
Indians	Omar et al 1985	866	WHO	>15	5.8	7.1	4.8
AUSTRALIA:							
Non-aborigines	*Glatthaar et al 1985	3197	WHO	≥25		4.3	3.3
Aborigines	*O'Dea et al 1988	148	WHO	35	16.4(<35yrs)	13.9(<35yrs)	18.6(<35yrs)
					34.8(≥35yrs)	44.4(≥35yrs)	28.6(≥35yrs)
TANZANIA	*McLarty et al 1989	6083	WHO	≥15	7.8	6.9	7.7
UNITED KINGDOM (LONDON)	*Forrest et al 1986	1040	WHO	>40	4.1		

* Information from Yudkin et al 1990

CHAPTER 3B

CLINICAL FEATURES OF THE CONTROL GROUP

PATIENTS AND METHODS

Sixty four Indian subjects volunteered to serve as controls for the study. They comprised healthy employees or relatives of employees from various departments at the University of Natal. These subjects were not known to have diabetes mellitus or any other medical disorder. As described in Chapter 2, they were age and weight matched to the study group, as closely as possible.

The following data were recorded from all the subjects studied:

(A) HISTORY:

1. Age, sex.
2. History of diabetes mellitus, hypertension, ischaemic heart disease, smoking, alcohol intake.
3. Family history of diabetes mellitus in a first-degree relative (defined as mother, father, sibling or off spring).

(B) CLINICAL EXAMINATION

1. Weight, height and Body Mass Index (BMI) which was calculated thus : $\frac{\text{Weight (Kg)}}{\text{Height (m)}^2}$
2. Blood pressure
3. Presence or absence of peripheral pulses.
4. Opthalmological examination for cataracts and evidence of retinopathy (as described in Chapter 2).

RESULTS

Results are shown in Table 1 - 3.

HISTORY: TABLE 1

31 males and 33 females were studied. The Mean Age was 42.5 ± 1.1 years; in males the Mean Age was 41.7 ± 2.1 years and in females 43.1 ± 1.9. years.

A positive history of diabetes mellitus in a first degree relative was obtained in 34 subjects (53.1%) - this was similar to that found in the study group (53.9%). A history of paternal diabetes (21.9%) was as common as that of maternal diabetes (20.3%), which was at variance with that found in the study group, in which a history of maternal diabetes (34.4%) was commoner than that of paternal diabetes (15.6%). As regards siblings, a history of diabetes amongst brothers and sisters, was

TABLE 1

CLINICAL CHARACTERISTICS - HISTORICAL INFORMATION

CONTROL GROUP AND STUDY GROUP AT YEAR 1

	CONTROL GROUP		STUDY GROUP		P
NUMBER	64		128		
MALE:FEMALE RATIO	31 : 33		67 : 61		
* AGE (YEARS)	42.5±1.4 (18-67)		48.5±1.1 (20-80)		ns
FAMILY HISTORY OF	n	%	n	%	
DIABETES:	34	53.1	69	53.9	
Father	14	21.9	20	15.6	0.04
Mother	13	20.3	44	34.4	0.007
Brothers	7	10.9	27	21.1	ns
Sisters	10	15.6	21	16.4	ns
Sons	0	0.0	2	1.6	ns
Daughters	1	1.6	0	0.0	ns

* Mean ± S.E. (Range)

ns = not significant

obtained in 7 subjects (10.9%) and 10 subjects (15.6%), respectively. Only 1 subject had an offspring (daughter) with diabetes - she had IDDM.

In order to validate this high prevalence of positive family history in the control subjects, details of a further 50 subjects (matched for sex and age) were analysed - these subjects were drawn from the group which had Normal Glucose Tolerance in the original survey (Omar et al 1985). Of these subjects, 56% gave a positive history of diabetes in a first degree relative.

BMI: TABLE 2 and 3

The Mean BMI of the control group of 24.3 ± 0.6 was similar to that of the study group (25.68 ± 0.6), as was expected.

BLOOD PRESSURE: TABLE 2 and 3

The Mean Blood Pressure of the control group was significantly lower than that of the study group $p < 0.001$. 3 subjects, all females, were found to have hypertension, and 2 of these 3 subjects had systolic blood pressure $\geq$ 150 mmHg.

PERIPHERAL PULSES AND OPTHALMOLOGICAL EXAMINATION: TABLE 2 and 3

None of the control subjects studied had evidence of peripheral vascular disease; 3 subjects had cataracts (all over 65 years).

TABLE 2

CLINICAL CHARACTERISTICS - CLINICAL EXAMINATION

CONTROL GROUP AND STUDY GROUP AT YEAR 1

	CONTROL GROUP	STUDY GROUP	P
NUMBER	64	128	
* AGE (YEARS)	42.5±1.4 (18-67)	48.5±1.1 (20-80)	ns
* WEIGHT (Kg)	65.6±1.7 (39-103)	66.5±1.1 (40-106.5)	
* HEIGHT (cm)	163.9±1.4 (140-192)	160.6±0.8 (140-180)	
* BMI	24.3±0.6 (14.7-35.6)	25.8±0.4 (16.8-40.7)	ns
OBESITY n (%)	20 (31.3)	54 (42.2)	
* BLOOD PRESSURE(mmHg)			
SYSTOLIC	116.7±2.4 (80-180)	129.9±1.8 (90-190)	<0.001
DIASTOLIC	73.6±1.3 (50-110)	81.4±1.2 (50-120)	<0.001
HYPERTENSION n (%)	3 (4.7)	22 (17.2)	
PERIPHERAL VASCULAR DISEASE	0	0	
OPTHALMOSCOPY (n)			
CATARACTS	3	7	
RETINOPATHY:			
diabetic	0	0	
hypertensive	0	6	

* Mean ± S.E. (Range)

ns = not significant

TABLE 3

CLINICAL CHARACTERISTICS OF THE CONTROL GROUP

	TOTAL	MALES	FEMALES
NUMBER	64	31	33
* AGE (YEARS)	42.5±1.4(18-67)	41.7±2.1(23-67)	43.1±1.9(18-66)
* WEIGHT (Kg)	65.6±1.7(39-103)	68.95±2.5(40-103)	62.4±2.3(39-91)
* HEIGHT (cm)	163.9±1.4(140-192)	171.6±1.7 (155-192)	156.98±1.2(140-171)
* BMI	24.3±0.6(14.7-35.6)	23.2±0.8(14.7-34.5)	25.3±0.9(16.3-35.6)
* OBESITY	20(31.3)	3(9.7)	17(51.5)
* BLOOD PRESSURE (mmHg)			
SYSTOLIC	116.7±2.4(80-180)	117.4±2.5(90-140)	116.1±4.0(80-180)
DIASTOLIC	73.6±1.3(50-110)	74.8±1.2(60-90)	72.4±2.3(50-110)
HYPERTENSION n (%)	3 (4.7)	0	3 (9)
PERIPHERAL VASCULAR DISEASE	0	0	0
OPTHALMOSCOPY (n)			
CATARACTS	3	0	3
RETINOPATHY:			
diabetic	0	0	0
hypertensive	0	0	0

* Mean ± S.E. (Range)

SUMMARY:

Sixty four Indian subjects (31 males and 33 females) were studied as the control group. The Mean Age of the group was 42.5 years. A positive history of diabetes was obtained in 53.1%. The Mean BMI was 24.3 and 31.3% were obese, obesity being more prevalent in females than males. The Mean Blood Pressure of the control group was $\frac{116.7}{73.6}$ mm Hg.

CHAPTER 4

CLINICAL FEATURES - ON THE BASIS OF GLUCOSE TOLERANCE AT YEAR 1

INTRODUCTION

Prospective studies on subjects with IGT (as described in Chapter 1), have demonstrated that such subjects may follow one of three courses: 1) persistence of IGT; 2) reversion to normal glucose tolerance; or 3) progression (worsening) to NIDDM; the significance of IGT being the latter risk. From the reported studies quoted in Chapter 1, the proportion of individuals with IGT who progress to NIDDM over a 10-year period varies from 13% - 61%, with a rate of progression of 1% - 5% per year (NDDG 1979).

The purpose of this study was to examine prospectively the natural history of IGT in 128 South African Indian subjects over a 4-year period.

According to the results of the oral G.T.T. at year 1, the subjects were divided into 3 categories of glucose tolerance; this chapter describes this division as well as some of the clinical features associated with these categories.

PATIENTS AND METHODS

BACKGROUND

As described in Chapter 1, 143 subjects were diagnosed as having IGT (according to WHO criteria), in an epidemiological survey (Omar et al 1985, unpublished data). Of these 128 subjects (67 males and 61 females) consented to participate in a prospective study from September 1985 - December 1988.

However, since the original study was an epidemiological one, only a modified O.G.T.T. was performed. More detailed description of clinical and biochemical profiles was not the purpose of that study. The clinical parameters examined in the original study included age, sex, family and personal history of diabetes, weight, height, BMI and Blood Pressure examination. Biochemical profiles included fasting and 2 hour post prandial plasma venous glucose, and in a subset of subjects, the plasma insulin levels.

However, a study such as the present one, necessitated a more detailed examination of the subjects. The subsequent follow-up of the subjects depended on their classification at year 1; therefore, central to the present study would be the findings at year 1, both in terms of the category of glucose tolerance as well as the clinical features in each of these categories.

Before pursuing this chapter, it would be important to clarify certain terminologies; since by the time that the present study was initiated, these 128 study subjects with IGT had already entered into the 2nd year of the natural history of their IGT.

Therefore reference to

Year 0		Year 1	
Year 1		Year 2	
Year 2	in the present study	Year 3	in a natural history
Year 3	corresponds to	Year 4	of subjects IGT
Year 4		Year 5	

METHODS:

1) At Year 1, a 75G Oral Glucose Tolerance Test (O.G.T.T.) (as described in Chapter 2) was performed on all 128 subjects with IGT (67 males and 61 females).

2) The following data were recorded in all the subjects:

(A) HISTORY:

1. Age, sex.
2. History of hypertension, IHD, smoking, alcohol.
3. Family history of diabetes mellitus.

(B) CLINICAL EXAMINATION

1. Weight, height and Body Mass Index (BMI) which was calculated thus: $\frac{\text{weight (Kg)}}{\text{height (M)}^2}$

2. Blood pressure.

3. Presence or absence of peripheral pulses.

4. Opthalmological examination for cataracts and evidence of retinopathy.

RESULTS

OGTT RESULTS: **Tables 1 - 3.**

Using the revised WHO criteria, the subjects were divided into 3 groups, according to the results of O.G.T.T. at Year 1:

IGT - the group which *persisted* with IGT.

Diabetes - the group which *progressed* to NIDDM

Normal - the group which *reverted* to Normal Glucose Tolerance.

Of the 128 subjects studied at Year 1,

47 *persisted* with IGT (36.72%)

41 *progressed* to NIDDM (32.03%)

40 *reverted* to Normal Glucose Tolerance (31.25%)

SEX: **Tables 1, 2, 3**

The sex distribution was similar for the IGT and normal groups i.e.. M:F 3:2, with a reversal of ratio for the Diabetes Group M:F 2:3. More females than males progressed to NIDDM. Of the 61 females with IGT who were followed up at Year 1 26(42.6%) progressed to NIDDM, 19(31.2%) persisted with IGT, and 6(26.2%) reverted to Normal Glucose Tolerance.

Of the 67 males studied, 15(22.4%) progressed to NIDDM, 28(41.8%) persisted with IGT and 24(35.8%) reverted to Normal Glucose Tolerance.

TABLE 1

CLINICAL CHARACTERISTICS - HISTORICAL INFORMATION OF STUDY GROUP AT YEAR 1, BASED ON CATEGORY OF GLUCOSE TOLERANCE

	IGT		DIABETES		NORMAL	
NUMBER	47		41		40	
MALE:FEMALE (n)	28:19		15:26		24:16	
(%)	60:40		37:63		60:40	
*AGE (YEARS)	48.5±1.5(25-77)		51.6±2.1(20-80)		45.4±2.0(20-75)	
PERSONAL HISTORY						
Diabetes Mellitus	0		0		0	
Hypertension	7		5		2	
IHD	3		1		2	
Smoking	13		13		16	
Alcohol	1		1		2	
FAMILY HISTORY	n	%	n	%	n	%
OF DIABETES MELLITUS	24	51.1	23	56.0	22	55.0
Father	7	14.9	8	19.8	5	12.5
Mother	16	34.0	13	31.7	15	37.5
Brother	8	17.0	9	21.6	10	25.0
Sister	7	14.9	10	24.4	4	10.0
Son	0	0.0	2	4.9	0	0.0
Daughter	0	0.0	0	0.0	0	0.0

*Mean + S.E. (Range)

TABLE 2

CLINICAL CHARACTERISTICS - CLINICAL EXAMINATION
STUDY GROUP AT YEAR 1, BASED ON CATEGORIES OF GLUCOSE TOLERANCE

	IGT	DIABETES	NORMAL	P
Number	47	41	40	
*Age (years)	48.5±1.5(25-77)	51.6±2.1(20-80)	45.4±2.0(20-75)	
*Weight (Kg)	67.7±1.5(40.2-97)	68.9±2.1(42.5-106.5)	62.8±1.9(43-92.5)	
*Height (cm)	162.7±1.3(140-180)	158.2±1.5(140-180)	160.8±1.4(142-176)	
*BMI	25.7±0.6(16.9-33.2)	27.6±0.8(18.4-40.7)	24.3±0.7(16.8-31.6)	+
Obesity n (%)	20(42.6)	21(51.2)	13(32.5)	
*Blood Pressure (mmHg)				
Systolic	130.2±2.9(110-190)	134.4±3.6(90-190)	125±2.7(100-180)	
Diastolic	81.9±2.0(60-120)	83.9±2.1(50-120)	78.3±1.9(60-110)	
Hypertension n (%)	7(14.9)	11(26.8)	4(10)	
P.V.D.	0	0	0	
Opthalmoscopy (n)				
Cataracts	0	7	0	
Retinopathy:				
Diabetic	0	0	0	
Hypertensive	3	2	1	

*Mean ± S.E. (Range)

+ Diabetes vs Normal $p < 0.001$

TABLE 3

CLINICAL CHARACTERISTICS - CLINICAL EXAMINATION

STUDY GROUP AT YEAR 1, BASED ON CATEGORIES OF GLUCOSE TOLERANCE

	IGT		DIABETES		NORMAL	
TOTAL (n)	47		41		40	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
n	28	19	15	26	24	16
%	59.6	40.4	36.6	63.4	60	40
*Age(yr)	48.1±2.2(25-77)	49.0±1.9(38-68)	51.8±2.9(33-73)	51.4±2.9(20-80)	46.9±2.7(22-75)	42.9±3.1(20-66)
*Weight(kg)	70.0±2.1(52.5-97)	64.3±2.0(40-80)	72.6±2.6(61-96)	66.7±2.9(42.5-106.5)	66.1±2.7(45.2-92.5)	57.8±2.6(43-77)
*Height(cm)	167.9±1.0(156-180)	154.9±1.7(140-172)	165.7±0.9(158-172)	153.9±1.7(140-180)	166.3±1.1(156-176)	152.4±1.6(142-166)
*BMI	24.8±0.7(18.3-32.9)	26.9±0.9(16.9-33.2)	26.4±0.9(21.6-35.2)	28.2±1.1(18.4-40.7)	23.8±0.9(16.8-31.6)	24.9±1.1(18.6-30.7)
obesity n(%)	7(25)	13(68.4)	5(33.3)	16(61.5)	6(25)	7(43.8)
*B.P.(mmHg)						
systolic	131.1±4.0(110-190)	128.9±3.9(110-160)	130±4.6(110-170)	136.9±4.9(90-190)	125.4±3.3(100-170)	124.4±4.8(110-180)
diastolic	81.3±2.7(60-120)	82.8±2.9(60-110)	84.7±2.6(70-100)	83.5±2.9(50-120)	79.6±2.5(60-110)	76.3±2.9(60-110)
Hypertension	4	3	3	8	3	1
Eyes:						
(i) cataract	0	0	3	4	0	0
(ii)retinopathy						
diabetic	0	0	0	0	0	0
hypertension	3	0	1	1	0	1

*Mean ± S.E. Range

AGE: **Tables 1 - 4**

The Mean Age was highest in the Diabetes group, compared to the other two groups; however, the difference was not significant.

With regards age distribution (Table 3), the majority in all 3 groups were $>$ 35 years; of the IGT group 95.7% were $>$ 35 years, whilst in the Diabetes and Normal group, 87.8% and 80%, respectively, belonged to this age group.

The age distribution was similar in males and females, in all 3 groups.

PERSONAL AND FAMILY HISTORY: **Table 1.**

A positive history of diabetes affecting a first degree relative was obtained in over 50% in all 3 groups. 50% of the subjects who gave a positive history of hypertension and ischaemic heart disease belonged to the IGT group. Of the four subjects who admitted to a history of alcohol intake; two had Normal Glucose Tolerance.

B.M.I.: **Tables 2,3,5 and 6**

The Mean BMI was highest in the Diabetes group, with a significant difference between this group and the Normal group $p<0.001$.
There was no significant difference in BMI between males and females, for each of the three groups studied.

TABLE 4

AGE DISTRIBUTION OF STUDY GROUP AT YEAR 1, BASED ON CATEGORIES OF GLUCOSE TOLERANCE

AGE GROUP	IGT		DIABETES		NORMAL	
(YEARS)	n	%	n	%	n	%
20 - 24	0	0.0	1	2.4	2	5.0
25 - 34	2	4.3	4	9.8	6	15.0
35 - 44	15	31.9	7	17.1	9	22.5
45 - 54	19	40.4	11	26.8	14	35.0
55 - 64	7	14.9	9	22.0	5	12.5
65 - 74	3	6.4	8	19.5	3	7.5
75 - 84	1	2.1	1	2.4	1	2.5
TOTAL	47	100	41	100	40	100
≥ 35	45	95.7	36	87.8	32	80.0

TABLE 5

BMI DISTRIBUTION OF STUDY GROUP AT YEAR 1, BASED ON CATEGORIES OF GLUCOSE TOLERANCE

BMI	IGT		DIABETES		NORMAL	
	n	%	n	%	n	%
15 - <21	5	10.6	2	4.9	10	25.0
21 - <25	17	36.2	12	29.3	11	27.5
25 - <27	8	17.0	8	19.5	7	17.5
27 - <30	10	21.3	6	14.6	9	22.5
≥30	7	14.9	13	31.7	3	7.5
TOTAL	47	100	41	100	40	100
OBESITY ≥27 males ≥25 females	20	42.6	21	51.2	13	32.5

TABLE 6

BMI DISTRIBUTION OF STUDY GROUP AT YEAR 1, BASED ON CATEGORIES OF GLUCOSE TOLERANCE

BMI	IGT (47)				DIABETES (41)				NORMAL (40)			
	male		female		male		female		male		female	
	n	%	n	%	n	%	n	%	n	%	n	%
15-<21	4	14.3	1	5.3	0	0.0	2	7.7	7	29.2	3	18.8
21-<25	12	42.9	5	26.3	4	26.7	8	30.8	5	20.8	6	37.5
25-<27	5	17.9	3	15.8	6	40.0	2	7.7	6	25.0	1	6.3
27-<30	5	17.9	5	26.3	4	26.7	2	7.7	5	20.8	4	25.0
≥30	2	7.1	5	26.3	1	6.8	12	46.2	1	4.2	2	12.5
TOTAL	28	100	19	100	15	100	26	100	24	100	16	100
OBESITY	7	25	13	68.4	5	33.3	16	61.5	6	25.0	7	43.8

≥27 males

≥25 females

The prevalence of obesity was high in all three groups; 51.2% of the Diabetes group, 42.5% of the IGT group and 32.5% of the Normal group were obese. With regards sex distribution, obesity was more prevalent in females than in males, in each of the groups.

BLOOD PRESSURE: **Tables 2 and 3**

The Mean Blood Pressure was highest in the Diabetes group, although the difference between this and the other two groups was not significant. The sex distribution was similar in each of the three groups.

Hypertension was found in 26.8% of the Diabetes group, compared to 14.9% and 10% in the IGT and Normal groups respectively.

Over 1/3 of the Diabetes group, had systolic blood pressure $>$ 150mmHg, compared to 17% and 10% in the IGT and Normal groups, respectively.

With regards sex distribution, in the Diabetes group, hypertension was more prevalent in females (30.7%) than in males (20%). In the IGT group, the sex distribution was similar i.e, M:F = 14.3% vs 15.8%; whilst in the Normal Group more males (12.5%) than females (6.3%) were hypertensive.

In each of the three groups studied, more females than males had systolic blood pressure $>$ 150mmHg.

PERIPHERAL PULSES AND OPTHALMOLOGICAL EXAMINATION **Table 2 and 5**

All the subjects studied had normal and palpable peripheral pulses. The seven subjects who had cataracts, belonged to the Diabetic Group.

None of the subjects had evidence of diabetic retinopathy. Of the 6 subjects who had evidence of hypertensive retinopathy, 3 belonged to the IGT group, 2 and 1, to the Diabetes and Normal Group, respectively.

SUMMARY

128 subjects with IGT (67 males and 61 females) had follow-up O.G.T.T. at year 1. Of these 47 persisted with IGT (36.72%), 41 progressed to NIDDM (32.03%) and 40 reverted to Normal Glucose Tolerance (31.25%).

42.6% of the females and 22.4% of the males studied, progressed to NIDDM. Of the males, 41.8% persisted with IGT and 35.8% reverted to Normal Glucose Tolerance. Of the females studied, 31.2% persisted with IGT and 26.2% reverted to Normal Glucose Tolerance.

The Mean Age was similar in all three groups. A positive family history of diabetes was found in over 50% in all three groups.

The Mean BMI was significantly higher in the Diabetes Group (27.6 ± 0.8) compared to the Normal Group (24.3 ± 0.7). Obesity, which was found in 51.2%, 42.5% and 32.5% of the Diabetes, IGT and Normal Groups respectively, was more prevalent in females than males in each of the three groups.
Hypertension was found in 26.8%, 14.9% and 10% of the Diabetes, IGT and Normal Groups respectively.

None of the subjects displayed evidence of microvascular complications viz diabetic retinopathy.

PATIENTS AND METHODS

BACKGROUND:

As described in Chapter 2, 143 subjects were diagnosed as IGT, according to WHO criteria, in an epidemiological survey (Omar et al 1985, unpublished data). Of these, 128 subjects (67 males and 61 females) consented to participate in a prospective study from September 1985 - December 1988.

Since the original study (to be referred to herewith as Year 0) was an epidemiological one, only a modified oral G.T.T. was performed i.e., fasting and 2 hour post-prandial plasma glucose levels after an overnight fast. A detailed description of clinical and biochemical profiles was not the purpose of that study.

However, a study such as the present one necessitated a more detailed examination of the subjects.

At the outset it would be important to clarify certain points of nomenclature; since, by the time the present study was initiated, these 128 study subjects with IGT had already entered into the 2nd year of the natural history of their IGT; therefore:

Year 0 in the present study corresponds to Year 1 in natural history of IGT in the subject

Year 0 Year 1 Year 2 Year 3 Year 4	in the present study corresponds to:	Year 1 Year 2 Year 3 Year 4 Year 5	in the natural history of IGT in the subjects

METHODS

(A) A two-hour 75G - oral glucose tolerance test (OGTT), was performed after an overnight fast, as described in Chapter 2. Briefly, fasting venous blood samples for plasma glucose were drawn, and within 5 minutes, 75G glucose dissolved in 250ml of water, was taken by mouth. After the first sip timed blood samples were drawn at 15, 30, 60, 90 and 120 minutes.

According to the results of the OGTT, at Year 1 the subjects were classified into 3 categories of glucose tolerance, using the revised WHO criteria (described in Chapter 2) viz. IGT, Normal Glucose Tolerance, and Diabetes Mellitus.

(B) 1) All the subjects in the study group (128) had OGTT performed at Year 1.

2) Further follow-up was determined by the category of glucose tolerance to which the subject belonged at Year 1.

a) The end point of study for any subject was the date of diagnosis of NIDDM.

b) Those subjects who, at Year 1, persisted with IGT or reverted to Normal Glucose Tolerance, were requested to undergo a repeat OGTT at Year 4.

3) In addition, a subgroup of those subjects who, at Year 1, persisted with IGT or reverted to Normal Glucose Tolerance, had follow-up O.G.T.T. at Year 2.
Again, the end point of study for any subject, was the development of NIDDM.

<u>RESULTS</u> Figure 1-3. Table I

YEAR 1 (1985) Figure I

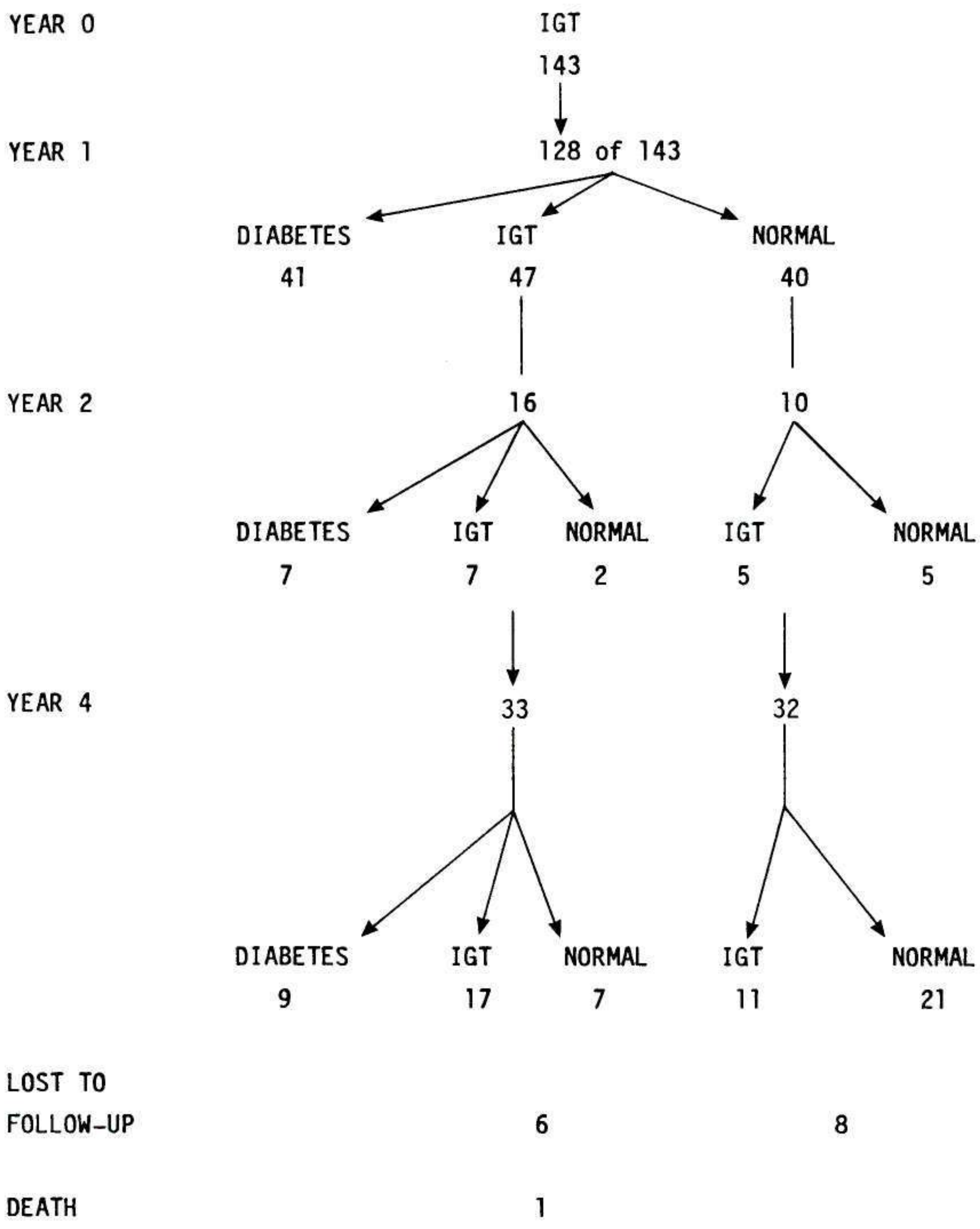
Of the 143 subjects who were eligible for study, 128 subjects consented to participate in this prospective study i.e., the initial response rate was 89.5%.

According to the results of OGTT at Year 1, the subjects were divided into 3 groups:

IGT_1 - the group which *persisted* with IGT.
$Diabetes_1$ - the group which *progressed* to NIDDM.
$Normal_1$ - the group which *reverted* to NORMAL Glucose Tolerance.

FIGURE 1.

FOLLOW-UP OGTT RESULTS OF IGT SUBJECTS OVER STUDY PERIOD



of the 128 IGT subjects studied at Year 1,

47 *persisted* with IGT (36.7%) - IGT_1

41 *progressed* to NIDDM (32.03%) and - $Diabetes_1$

40 *reverted* to NORMAL Glucose Tolerance (31.25%) - $Normal_1$

YEAR 2 (1986) Figure 1,2

At Year 2, 26 subjects (16 IGT_1 and 10 $Normal_1$) had O.G.T.T. performed.

Of the 16 IGT_1, 7 subjects progressed to NIDDM (43.8%), 7 persisted with IGT (43.8%) and 2 reverted to Normal Glucose Tolerance (12.5%).

Of the 10 Normal subjects, 5 persisted with Normal Glucose Tolerance whilst 5 reverted to IGT. None of the $Normal_1$ subjects progressed to NIDDM at Year 2.

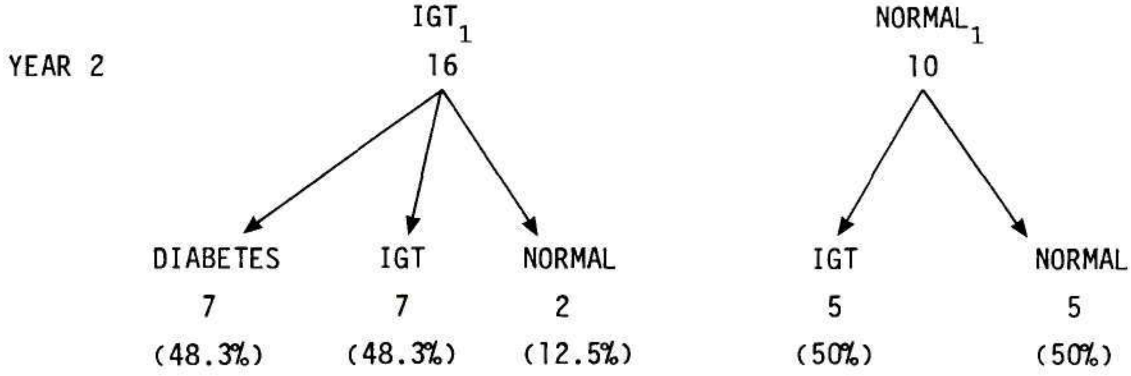
YEAR 4 (1988) Figure 1 & 3 Table 1

At Year 4, which was the last year of this study, 80 subjects were eligible for follow-up examination i.e., those belonging to IGT_1 (40 subjects) and $Normal_1$ group (40 subjects). 65 of these 80 subjects consented to the repeat examination i.e., response rate of 81.3%.

Of the 40 IGT_1 subjects eligible for examination at Year 4, 33 consented; 1 subject died in the interim (ruptured aortic aneurysm), 5 refused further follow-up and 1 subject could not be traced.

FIGURE 2.

FOLLOW-UP OGTT RESULTS IN STUDY GROUP AT YEAR 2



Of the 40 $Normal_1$ subjects eligible for follow-up at Year 4, 32 subjects consented, 5 refused and 3 could not be traced.

(a) At Year 4, of the 33 IGT_1 subjects followed up;
9 (27.3%) *progressed* to NIDDM
17 (51.5%) *persisted* with IGT
and 7 (21.2%) *reverted* to Normal Glucose Test.

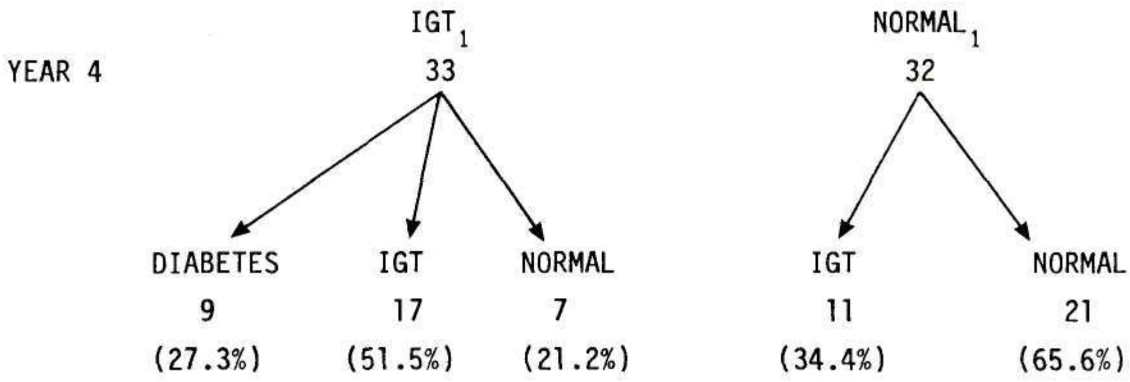
2 of the subjects who persisted with IGT at Year 4, had in fact reverted to Normal Glucose Tolerance at Year 2, whilst 2 of the subjects who reverted to Normal at Year 4, had persisted with IGT at Year 2. None of the 9 IGT_1 subjects who had O.G.T.T. both at Year 2 and 4 progressed to NIDDM.

(b) Of the 32 $Normal_1$, subjects followed up at Year 4,
11 (34.4%) *reverted* to IGT
21 (65.6%) *persisted* with NORMAL Glucose Tolerance
None of these subjects *progressed* to NIDDM.

2 of the subjects who progressed to IGT at Year 4 had persisted with Normal Glucose Tolerance at Year 2, whilst 1 subject who persisted with Normal Glucose Tolerance at Year 4 had in fact progressed to IGT at Year 2.

FIGURE 3.

FOLLOW-UP OGTT RESULTS IN STUDY GROUP AT YEAR 4



OVERALL RESULTS BY YEAR 4

Table 1 and Figure 1

Of the 128 subjects with IGT who participated in this prospective study at Year 1 (1985), 113 subjects satisfactorily completed the study, either by returning for follow-up O.G.T.T. (those who were IGT_1 or $Normal_1$), or because they had reached the end-point of study (date of diagnosis of NIDDM at any point). Thus the response rate in this study was 88.3%.

By Year 4 (Table 1), of the 113 subjects with IGT who had satisfactorily completed the study,

57 *progressed* to NIDDM (50.4%)

28 *persisted* with IGT (24.8%) and

28 *reverted* to NORMAL Glucose Tolerance (24.8%).

Thus the rate of progression to NIDDM was **12.6%** per annum.

[On the other hand if all 128 subjects with IGT who were originally entered into the study are analysed, the results are as follows:-

57 *progressed* to NIDDM (44.5%)

28 *persisted* with IGT (21.9%)

28 *reverted* to Normal Glucose Tolerance (21.9%)

15 did not return for follow-up after Year 1 (11.7%)

Thus, the rate of progression to NIDDM, is 11.1%, when all 128 subjects are evaluated.]

TABLE 1.

OUTCOME OF STUDY SUBJECTS BY YEAR 4

DIAGNOSIS AT YEAR 1	GLUCOSE TOLERANCE BY YEAR 4 DIABETES	IGT	NORMAL	NO FOLLOW UP	DEATHS
$DIABETES_1$ (n=41)	41				
IGT_1 (n=47)	16 (7 at Yr 2, 9 at Yr 4)	17	7	6	1
$NORMAL_1$ (n=40)	0	11	21	8	
	57	28	28	14	1

57 + 28 + 28 = 113

14 + 1 = 15

113 + 15 = 128

TABLE 2.

PROGRESSION (WORSENING) TO NIDDM IN SUBJECTS WITH IGT IN VARIOUS POPULATION GROUPS

STUDY (AUTHORS)	% WHICH PROGRESSED	DURATION OF STUDY (YRS)	RATE OF PROGRESSION PER ANNUM (%)
WHITEHALL (Jarrett et al)	13.2	5	2.6
BEDFORD (Keen et al)	15.0	10	1.5
TOKYO (Kadowaki et al)	16.7		
NAURU (King et al)	26.0	6	4.0
SWEDEN (Sartor et al)	29.0		
OSAKA (Sazaki et al)	38.5		
BIRMINGHAM	45.0	10	4.5
U.S.A. (O'Sullivan and Mahan)	52.5	1-12	5.0
U.S.A. (Bennett)			3.0
PIMA INDIANS (Saad et al)	*31.0	+1.6-11.0	5.0-6.0
MALTA (Schrantz)	31.0	6	5.0

* 25% at 5 years
61% at 10 years

\+ 1.6 - 11.0 (median 3.3) years

DISCUSSION

The relatively recent introduction of the category of IGT as a distinct entity (NDDG 1979, WHO 1980, 1985), was based on the results of a few long term prospective studies in Britain and U.S.A. (O'Sullivan and Mahan 1968; Birmingham Diabetes Survey Working Party 1976; Jarrett et al 1979; Keen et al 1982; Jarrett et al 1982).

The significance of IGT lies in the fact that prospective studies, albeit a few, have highlighted the following risks:

1) Progression to NIDDM (O' Sullivan and Mahan 1968; Birmingham Diabetes Survey Working Party 1976; Jarrett et al 1979; Keen et al 1982; Sartor et al 1980; Jarrett et al 1982; Sazaki et al 1982; King et al 1984; Kadowaki et al 1984; Saad et al 1988).

2) Increased risk for developing macrovascular disease (Fuller et al 1980; Jarrett and Keen 1976; Jarrett et al 1982). Of particular interest is the paucity of microvascular complications such as retinopathy and nephropathy in subjects with IGT (Jarrett and Keen 1976; Jarrett et al 1979; NDDG 1979).

As regards the risk of progresion to NIDDM, prospective studies have demonstrated that subjects with IGT may follow one of three courses; 1) persistence of IGT; 2) reversion to Normal Glucose Tolerance; or 3) progression (worsening) to NIDDM. From reported studies quoted above (Table 2), the proportion of individuals with IGT who progress to NIDDM over a 10 year period varies from 13% - 52%, with a rate of progression of 1% - 5% per annum (NDDG 1979).

Prospective studies of subjects with IGT may provide clues as to the aetiology and pathogenesis of Diabetes Mellitus. Moreover, in order to determine the significance of IGT with respect to its pathophysiological basis and prognostic implications in different populations, it is vital that prospective population-based studies on IGT be performed. However, as cited above, only a few reports on longitudinal studies of IGT exist in the literature. It is therefore not surprising that there has been a call from the WHO Expert Committee on Diabetes (1980, 1985) for further population-based studies of IGT, in an attempt to shed further light on the validity of this entity (as well as to provide evidence concerning the present diagnostic criteria for Glucose Tolerance).

In the present study on South African Indians with IGT, 50.4% of the subjects progressed to NIDDM over a 4 year period, with a rate of progression of 12.6% per annum.

However, as emphasised earlier, comparison with earlier data recorded in the literature, is hampered by differences in methodology and diagnostic criteria employed in those studies.

In a prospective study in the USA (O'Sullivan and Mahan 1968), 352 non-pregnant adult females with chemical diabetes were followed up for 1-12 years. Of these subjects, 25.9% were later diagnosed as having Diabetes Mellitus, 45% reverted to Normal Glucose Tolerance, and 30% remained in the initial impaired tolerance category. Using life-table calculations, it was found that 52.5% of these subjects would have progressed to decompensation of carbohydrate control within 10 years of diagnosis of chemical diabetes, with a rate of progression of 5% per annum.

However comparison with that study is hampered by the diagnostic criteria employed. The diagnosis of chemical diabetes was based on USPHS criteria viz. 3 or more of the following, parameters: fasting glucose level >110mg/dl (6.1mmol/L), 1 hour level >170mg/dl (9.4mmol/L), 2 hour level 120mg/dl (6.7mmol/L) and ; 3 hour level >110mg/dl (6.1mmol/L); The diagnosis of unequivocal diabetes was based on 2 or more of the following levels: blood glucose >300mg/dl (16.7mmol/L) at any time within 3 hours after 100G oral glucose, blood glucose >180mg/dl (10mmol/L) within 5 hours of a meal; and fasting blood glucose ≥ 120mg/dl (6.7mmol/L).

Thus if the above criteria were employed, in the present study many more subjects would have been labelled as "IGT" at the outset. The criteria for the diagnosis of diabetes employed in the above study precludes any comparison between that and the present study.

Notwithstanding the above limitations in terms of comparison, it is important that the quoted study was one of the first to highlight the increased risk of progression to unequivocal diabetes in subjects with chemical diabetes.

In the present study, 50.4% of the subjects with IGT progressed to NIDDM over a 4 year period, with a rate of progression of 12.6% per annum. [Even if the response rate were taken into consideration i.e., initial response rate 90% (128 of 143 eligible subjects) and subsequent completion of the study in 113 subjects,-the risk of progression to NIDDM is still high - 40% (57/143) with a rate of progression of 8% per annum.] Therefore in this population, the diagnosis of IGT may have more serious prognostic implications and cannot be ignored. Of importance, would be the identification of risk factors for worsening to diabetes.

The second study quoted above was a 10 year follow-up study undertaken by the Birmingham Diabetes Survey Working Party (1976) in the United Kingdom. In this study, 808 subjects had 50G O.G.T.T. performed at baseline - the subjects were classified as diabetes, normal, borderline (GTT diabetes) and the remainder of individuals were classed into several groups with minor degrees of Glucose Tolerance. Those subjects with overt diabetes were referred to their physicians, whilst those in the other categories were told that they were normal and no treatment was advised. It was the latter subjects who were followed-up at 5 and 10 years after the original test. At 10 years, 382 subjects had repeat O.G.T.T. (83% of those still alive and available for testing). At 10 years, of the 31 subjects who were originally classified as GTT diabetes, 45% (14 subjects) progressed to overt diabetes, 23% (7 subjects) remained unchanged, 32% (10 subjects) reverted to normal (2 subjects) or had minor glucose abnormalities (8 subjects). Thus, the average rate of decompensation of GTT diabetes to overt diabetes in that study was 4.5% per annum. None of the subjects who had Normal Glucose Tolerance in the original study progressed to Diabetes at the follow-up.

Comparison between the above study and the present one is again hampered by the diagnostic criteria employed. In the Birmingham Study, 50G oral G.T.T.'s were performed - GTT diabetes was based on a fasting blood glucose (capillary) whole blood $<$7.2mmol/L and a 2 hour level $>$7.5mmol/L, with a 1 hour level $>$10mmol/L. Overt diabetes was diagnosed in those subjects whose fasting blood glucose exceeded 7.2mmol/L. Normal Glucose Tolerance was based on fasting glucose $<$5.6, 1 hour $<$10, and 2 hour $<$ 7.5 mmol/L.

In addition, whilst 45% of GTT diabetics progressed to overt diabetes in the Birmingham Study, it must be noted that the actual number studied was small i.e., only 31 of the 393 subjects who were retested at 10 years, were originally defined as GTT diabetics (7.9%).

Nevertheless, the above study was important for several reasons. Firstly, it highlighted the significance of the category of GTT diabetes with regard to progression to overt diabetes; secondly higher 2 hour blood glucose levels (7.5 mmol/L vs 6.7 mmol/L) were adopted for the diagnosis of GTT diabetes, arising from the finding in their 5 year follow-up study, that regardless of the original GTT category, nearly all these subjects who progressed to florid diabetes, had 2 hour blood glucose levels $>$7.5mmol/L in the first test. (Birmingham Diabetes Survey Working Party 1970). Thirdly, the results of that study suggested that Normal Glucose Tolerance could be redefined at a higher 2 hour blood glucose level of $<$7.5mmol/L (vs 6.7mmol/L used previously). In addition, since in that study, the 10 year mortality was low in subjects with GTT diabetes, it was proposed that the options in management of such subjects include either treatment with oral hypoglycaemic agents (in the hope of preventing progression to diabetes), or yearly review (so that the florid state may be recognised and treated as soon as possible). Thirteen years later and after a few more prospective studies, little has changed with respect to the originally proposed recommendations for the management of IGT subject. Finally, in the Birmingham Study, it was found that no striking differences emerged as a result of the 10 years of follow-up, as opposed to the 5 year follow-up. Whilst the proportion of retested subjects developing both florid and GTT diabetes had increased, it had not doubled between 5 years and 10 years. Moreover, that with longer periods of follow-up, the loss of subjects for various reasons during this period, may actually prevent a meaningful result.

The third long term study, was the Bedford Study in the United Kingdom (Keen et al 1982). In this well designed, 10 year prospective study (1962-1972), the diagnosis of IGT was based on 2 hour capillary blood glucose level 6.7 mmol/L - 11.1 mmol/L, using a 50G oral G.T.T. Of 241 subjects with IGT who were followed up, 15% (36 subjects) worsened to diabetes, 53% (128 subjects) reverted to Normal Glucose Tolerance, 22.8% (55 subjects) persisted with IGT, and 9% (22 subjects) remained uncategorised. The average rate of worsening to diabetes (w.t.d.) was 1.5% per annum. Of the many variables analysed, the major predictor of w.t.d., was the level of blood glucose at baseline. BMI, whilst not a predictor for w.t.d., in the first 5 years, was an independent and significant risk factor during the second 5 years. In addition, in the Bedford Survey, the subjects were randomly assigned to 4 treatment groups based on 2 x 2 design - tolbutamide or placebo tablet; dietary CHO restriction or simple restriction of table sugar.

However, the effects of treatment (tolbutamide and/or dietary CHO restriction) had no significant effect on glucose tolerance.

In another British Study viz: the Whitehall Study (Jarrett et al 1979; Jarrett et al 1977), of the 204 male civil servants who were diagnosed as IGT and who were followed up for 5 years, 13.2% (27 subjects) worsened to diabetes. Of the baseline variables studied, only the blood glucose values were significantly predictive of w.t.d. As in the Bedford Study, the subjects were randomly allocated to one of 4 treatment groups: 120G/day CHO diet + placebo; 120G/day CHO diet + 50mg phenformin; limited sucrose (table sugar) intake + 50mg phenformin. Treatment had no significant effect on glucose tolerance in the Whitehall Study.

The Whitehall Study and the present one are not strictly comparable because of different methods and criteria employed. In that study, 50G oral G.T.T., was performed in the afternoon, and as stated previously (NDDG 1979, WHO 1980, Bennett 1983, Zimmet P 1982), this may interfere with results due to possible diurnal variations in blood glucose levels. The criteria for diagnosis of IGT was based on (i) a screening capillary blood glucose 6.1 - 11.1 mmol/L 2 hours after 50G oral glucose; and (ii) at O.G.T.T., a peak blood glucose ≥ 10mmol/L and 2 hour level of 6.7 - 11.1 mmol/L and/or 2 values ≥10mmol/L and/or Mean 2 hour blood glucose levels (screening and G.T.T.) > 6.7mmol/L. Moreover, the diagnosis of Diabetes was based on arbitrary criteria viz. (i) 2 successive or 3 non-successive 2 hour post 50G glucose capillary blood glucose level >11.1mmol/L; (ii) 2 hour blood glucose >11.1mmol/L at O.G.T.T. performed on the 10th visit, irrespective of whether previous 2 hour values were also elevated; (iii) unequivocal symptoms or signs of diabetes mellitus.

In the present study, a 75G oral G.T.T., was performed in the morning, and even at the baseline screening test (Year 0), subjects had both fasting and 2 hour blood glucose levels done. Of historical interest, is that the authors of the Whitehall Study suggested that the descriptive term of IGT be coined in order to avoid the word diabetes with all its implication.

In summary each of the 4 studies quoted above, were done in different population groups, selected in different ways, and differing in the methods used and in the criteria adopted for defining worsening to diabetes. Nevertheless, the single point that emerged was that the levels of blood glucose themselves, however defined, best predict subsequent worsening to diabetes.

Studies more comparable to the present one, with respect to methodology and criteria employed, include the studies on the Natural History of IGT in Pima Indians and Nauruans, two-populations with the highest prevelance of Diabetes Mellitus and IGT, respectively (Bennett et al 1971, Knowler et al 1978, Zimmet et al 1982).

In the follow-up study of 384 Pima Indian with IGT over a period of 1.6 - 11.5 years (Saad et al 1988), 31% (118 subjects) progressed to NIDDM, 26% (100 subjects) persisted with IGT, and 43% (166 subjects) reverted to Normal Glucose Tolerance. The cumulative incidence of NIDDM in that study was 25% and 61% at 5 years and 10 years, respectively (rate of progression 5% - 6% per annum). The risk factors for progression to NIDDM were age below 40 years, after which age had a beneficial effect; higher baseline plasma glucose levels (both fasting and after CHO load); higher serum insulin levels after fasting; lower insulin levels after CHO loading.

Thus the finding in the present study, that 50.4% of South African Indian subjects with IGT progressed to NIDDM (rate of progression 12.6% per annum) is even higher than that found in the Pima Indians. The proportion of subjects who persisted with IGT, 24.8%, is similar to that found in the Pima Indians (26%), whilst fewer subjects (24.8%) reverted to Normal Glucose Tolerance in the present study, compared to the Pima Indian Study, in which 43% reverted to Normal Glucose Tolerance.

The results of the present study are at variance with most other reported prospective studies of subjects with IGT, which report that in less than half, the abnormality progresses to NIDDM within 10 years; and that in the majority, glucose tolerance reverts to normal or remains unchanged. (Birmingham Diabetes Survey Working Party 1976, Keen et al 1982, Sartor et al 1980, NDDG 1979, Saad et al 1988).

Findings similar to those in Pima Indians were reported in a 6 year follow-up study of 51 Nauruan subjects with IGT (King et al 1984). In that study, 26% (13 subjects) progressed to NIDDM, 35% (18 subjects) persisted with IGT and 39% (20 subjects) reverted to Normal Glucose Tolerance; the crude rate of progression to NIDDM was 4% per annum. Of nine factors studied, the only significant predictive risk factor for w.t.d., was the baseline plasma glucose levels (both fasting and 2 hour post CHO load). Hence, again, the majority of subjects with IGT reverted to Normal Glucose Tolerance or persisted with IGT; less than 1/3 progressed to NIDDM.

In a 7 year follow-up of 13 Japanese subjects with IGT, 38.5% (5 subjects) progressed to NIDDM, 23.1% (3 subjects) persisted with IGT and 38.5% (5 subjects) reverted to Normal Glucose Tolerance (Sazaki et al 1982). However, the obvious limitation in that study was the sample size, making comparison difficult; in addition, 50G oral G.T.T. were performed.

In another Japanese study, 288 subjects with IGT were followed up for 5 - 12 years (Kadowaki et al 1984). 16.7% (48 subjects) progressed to NIDDM during the study period, and significant risk factors for subsequent w.t.d., included baseline plasma glucose levels (fasting and 2 hour levels), high maximal body weight index, and a diminished insulin response. However, in that study glucose tolerance was based on 100G oral G.T.T. and the diagnostic criteria employed were those of the Japan Diabetic Society, which differs from WHO criteria; in addition the study population was clinic based. All these factors make comparison between that and the present study difficult.

A 10 year follow-up study was performed on 267 Swedish men with IGT (Sartor et al 1980); that study also examined the effects of tolbutamide and diet regulation on prevention of development of Diabetes. At follow-up, 29% of 59 subjects on no treatment (17 subjects) progressed to NIDDM; whilst none of the 23 subjects (23 of

49 subjects) who were commenced on tolbutamide and diet regulation, progressed to NIDDM. However, different diagnostic criteria employed in that study make comparison with thepresent one somewhat difficult.

In a 6 year longitudinal study in Malta (Schrantz A.G. 1989), of the 75 subjects with IGT (35 males and 40 females), 30.7% progressed to NIDDM, 36% persisted with IGT, and 33% reverted to Normal Glucose Tolerance; the rate of progression was 5.1% per annum. The principal predictors of future NIDDM in that study, were age (>50 years), baseline plasma glucose levels (fasting level >5.5mmol/L and 2 hour level >9.5mmol/L) and initial BMI (>27Kg/M^2). The findings in the Maltese Study were consistent with those of the other studies quoted i.e., the majority of IGT subjects either persisted with IGT or reverted to Normal Glucose Tolerance.

An interesting finding in the present study, was the variability of O.G.T.T., results in the same patient, at the various stages of the study. In most other reported longitudinal studies, each subject had 2 O.G.T.T., - at baseline and at end-point of the study, but no GTT was performed in the interim period. In the present study, O.G.T.T., was performed at Year 0, Year 1, and Year 4 and a subset of the subjects also had O.G.T.T. at Year 2. 2 subjects who were classified as IGT at Year 1 and who persisted with IGT at Year 4, had in fact reverted to normal at Year 2; whilst 2 such subjects (IGT_1) who reverted to normal at Year 4, had persisted with IGT at Year 2. 2 subjects who were classified as normal at Year 1, and who progressed to IGT at Year 4, had Normal Glucose Tolerance at Year 2, whilst one such subject ($Normal_1$) who remained normal at Year 4, had in fact progressed to IGT at Year 2. The significance, if any, of this finding, is unknown. Owing to the lack of reported data on the variability of OGTT in long term studies of IGT, comparison is not possible.

In the present study, the finding that 50.4% of South African Indians with IGT progressed to NIDDM over a 4 year period (rate of progression 12.6% per annum) is one of the highest recorded in the literature. Therefore, in this population group, IGT (in otherwise healthy and ambulatory individuals) has significant prognostic implications and should not be ignored or taken lightly.

SUMMARY

A 4 year prospective study was undertaken on 128 South African Indian subjects with IGT which was diagnosed at Year 0.

At Year 1, 32% (41 subjects) *progressed* to NIDDM, 37% (47 subjects) *persisted* with IGT and 31% (40 subjects) *reverted* to Normal Glucose Tolerance; the subjects were divided into 3 groups according to the category of Glucose Tolerance at Year 1 viz. IGT_1, $Diabetes_1$, $Normal_1$.

At Year 2, 26 subjects (16 IGT_1 and 10 $Normal_1$) had O.G.T.T. Of the IGT_1 subjects, 43.8% (7 subjects) progressed to NIDDM. None of the $Normal_1$ subjects progressed to NIDDM.

At Year 4, 65 subjects (33 IGT_1 and 32 $Normal_1$) had follow-up O.G.T.T. Of the IGT_1 group, 27.3% (9 subjects) progressed to NIDDM, 51.5% (17 subjects) persisted with IGT and 21% (7 subjects) reverted to Normal Glucose Tolerance. Of the $Normal_1$ group 42% (11 subjects) progressed to IGT, 66% (21 subjects) persisted with Normal Glucose Tolerance and none progressed to NIDDM.

By Year 4, of the 128 subjects with IGT who had entered into the study, 113 satisfactorily completed the study. Of these 50.4% (57 subjects) progressed to NIDDM at Year 1, 2 or 4; 24.8% (28 subjects) persisted with IGT and 24.8% (28 subjects) reverted to Normal Glucose Tolerance.

The crude rate of progression to NIDDM was 12.6% per annum.

CHAPTER 6

INSULIN RESPONSE DURING OGTT AT YEAR 1

INTRODUCTION

Prospective studies on subjects with IGT have demonstrated that this entity is associated with an increased at risk for the development of diabetes mellitus (NDDG 1979, WHO 1980, 1985). Therefore, the study of the various biochemical characteristics of IGT could possibly lead to an understanding of the pathogenesis of NIDDM.

Since the development of a sensitive and specific radioimmunoassay for insulin (Yalow RS and Berson SE 1960), there have been numerous studies describing the patterns of insulin response to a secretagogue viz. glucose.

As regards the significance of studying insulin response in IGT, several points emerge from the literature:

1) heterogeneity of plasma insulin response appears to be common.
2) insulin response could serve as a marker for the subsequent deterioration to NIDDM in subjects with IGT.

Prior to literature review however, a few of the terms employed deserve comment : 1) *insulin concentration* reflects pancreatic B-cell response (*secretory function*) (Lillioja et al 1988); 2) *impaired insulin action* = insulin resistance, which may be reflected by elevated plasma insulin concentrations during fasting (especially in the presence of normal fasting plasma glucose levels), as well as during OGTT (Lillioja et al 1988, Saad et al 1988, Nagulesparan et al 1979, Hollenbeck et al 1984, Lillioja et al 1987).

There have been numerous descriptions regarding the pattern of insulin response during OGTT in subjects with IGT. Controversy existed as to whether hypo-or hyperinsulinaemia following an oral glucose load, is characteristic of subjects with mild or moderate glucose intolerance (Savage et al 1975). Earlier studies had reported decreased insulin response to oral glucose in subjects with borderline CHO intolerance (Cerasi et al 1973, Colwell JA and Lein A 1967), but these reports were challended by others who reported hyperinsulinaemia in such subjects (Reaven et al 1971, Rosenbloom A 1970, Jackson et al 1972, Chiles et al 1970, Danowski et al 1973).

However, in a study over a wide spectrum of glucose tolerance in Pima Indians, it was found that 2-hr plasma insulin levels were highest in the borderline group and lowest in the diabetes group, whilst fasting plasma insulin levels were similar in all groups - the conclusion was that their data could not support the concept of either hypo-or hyperinsulinaemia as the initial lesion in diabetes (Savage et al 1975). Of greater importance was the finding of a marked variation in insulin response and hence the emergence of the concept of "heterogeneity" of insulin response in borderline diabetes, a finding which was subsequently confirmed by other workers (Fajan et al 1974, Reaven GM and Olefsky JM 1977), Kosaka K and Akunama Y 1980, Ratzmann et al 1983).

Much of the earlier controversies could possibly be explained by the wide range of diagnostic criteria employed for glucose tolerance.

More recently, a study on insulin action and secretion in Pima Indians representing a wide spectrum of glucose tolerance, demonstrated that IGT in this population was primarily due to impaired insulin action and that subjects with IGT have insulin resistance and normal pancreatic secretory function, whilst subjects with NIDDM have both impaired insulin action and pancreatic secretory failure (Lillioja et al 1988).

In a study which examined the natural history of IGT in Pima Indian (Saad et al 1988), it was demonstrated that IGT subjects were characterised by hyperinsulinaemia and insulin resistance, thus confirming the findings of other workers that in IGT, there exists hyperinsulinaemia (Savage et al 1975, Reaven and Miller 1968, Zimmet et al 1978, Martin et al 1980) and insulin resistance (Lillioja et al 1988, Nagulesparan et al 1980, Reaven and Miller 1979, Reaven et al 1976).

With respect to insulin response serving as a predictor for subsequent deterioration to NIDDM in IGT subjects, Saad et al (1988) found that in Pima Indians, subjects with IGT who progressed to NIDDM had higher fasting serum insulin levels and ratios of fasting insulin to glucose levels, and thus presumably had a greater degree of insulin resistance than those who did not progress to NIDDM. In addition, such subjects (i.e. those who w.t.d.) also had 1) lower serum insulin levels after CHO loading; 2) lower ratio of insulin to glucose levels after CHO loading and 3) lower ratio of increment of insulin to increment of glucose post CHO loading, suggesting that their insulin responses to a CHO load were less adequate than in those subjects whose IGT did not progress to NIDDM. These findings supported data reported by other workers (Kadowaki et al 1984, Sicree et al 1987, Kosaka et al 1977, 1980). Saad's observations suggest that subjects with IGT destined to w.t.d are characterised by a higher degree of insulin resistance (with fasting hyperinsulinaemia) and a lower B-cell response to glucose, than those whose abnormality either persists or reverts to Normal; and that the development of NIDDM in subjects with IGT is determined by the interplay between those two abnormalities.

It appears that in the presence of insulin resistance, when the B-cells fail to respond appropriately and sufficiently to ingested CHO, the degree of glycaemia increases, insulin responses diminish further, and NIDDM ensues. This inadequacy of the beta-cell response may be attributed to inadequate beta-cell mass, the exhaustion of beta-cells, or the deleterious effect of minimal long-term elevations of blood glucose on those cells (Hollenbeck et al 1984).

Only two studies on insulin secretion in South African Indian subjects with IGT exist in the literature (Omar et al 1986, Jialal et al 1986), the first quoted being the baseline study from which subjects for the present study were selected; in the second study which was a hospital based survey, no difference was found in mean insulin responses and incremental insulin areas between IGT and control subjects.

In the present study (Chapter 5) the risk for subsequent progression to NIDDM is high; thus it would be vital to examine plasma insulin responses, to determine the pattern of response as well as to establish whether plasma insulin is a risk factor for progression to NIDDM in South African Indian subjects with IGT.

This chapter describes the insulin response to 75G oral GTT in the study subjects at Year 1.

PATIENTS AND METHODS

BACKGROUND:

Please refer to Chapters 2 - 5 re background

SUBJECTS:

The study group comprised 128 Indians subjects (67 males and 61 females) who were previously diagnosed as having IGT (as described in Chapters 2 - 5).

64 adult Indian subjects (31 males and 33 females) who were matched for age, sex and BMI, served as controls for the study (as described in Chapters 2 and 3b).

METHODS:

1) At Year 1, a two-hour 75G oral glucose tolerance test (OGTT) and insulin response to glucose load, was performed after an overnight fast, on all the study and control subjects, as described in Chapter 2.

Briefly. fasting venous blood samples for plasma glucose and insulin were drawn, and within 5 minutes, 75G glucose dissolved in 250ml of water was ingested. After the first sip, timed blood samples were drawn at 15, 30, 60, 90 and 120 minutes. Plasma glucose levels were determined by a glucose oxidase method and plasma insulin was determined by Radioimmunoassay using the double antibody technique (Phadeseph Kits).

According to the results of the OGTT at Year 1, the study subjects were classified into 3 categories, based on WHO criteria viz, IGT_1 $Normal_1$ $Diabetes_1$ (as described in Chapter 2).

Because of missing values, 4 control subjects were excluded from the statistical analysis, with a resultant 60 control subjects (28 males and 32 females) available for analysis.

2) For the purpose of analysis, both the stdy and control subjects were further divided, according to Body Mass Index (BMI) into "obese" and "non-obese" categories (please see Chapter 2).

3) In addition to plasma insulin response during OGTT, the following ratios and estimates of insulin response were examined:

I Insulinogenic Index II; $\left(\frac{\Delta \text{ insulin}}{\Delta \text{ glucose}}\right)$

II Ratio fasting insulin/glucose

III Ratio post load insulin/glucose

IV Ratio post load insulin/fasting insulin

V Area under the plasma insulin curve

I <u>Insulinogenic Index</u> $\left(\frac{\Delta \text{ insulin}}{\Delta \text{ glucose}}\right)$

was obtained by dividing the plasma insulin increments above the fasting value, by the corresponding net increase in plasma glucose, as described by Seltzer (1967). According to Seltzer, this empirical "index of insulinogenic reserve" serves as a measure of the insulin secretory response.

IV <u>Area under the plasma insulin curve during OGTT</u>: (μu/ml·hr)
was computed using the following formula:

$$\text{Area } (\mu u/ml \cdot hr) = 1/4\ (a+e) + \tfrac{1}{2}\ (b+c+d)$$

where a-e represent insulin values at 0, 30, 60, 90 and 120 minutes, respectively. (Reaven and Miller 1968, and personal communication with Professor G.M. Reaven). The above formula employs the method of trapezoid.

Insulin Area during OGTT has been found to correlate well with insulin resistance, as measured by insulin clamp technique (Hollenbeck et al 1984).

RESULTS

Results shown in Figure 1 - 9; Table 1 - 27

The results will be discussed under the following headings:

I Plasma Insulin Response during OGTT

II Insulinogenic Index

III Insulin Ratios

IV Area under the Plasma Insulin curve

V Logs of I - IV

VI Correlation Analysis

For each variable to be discussed, the study subjects will be divided and compared to the control group as follows:

A. Total study group (128 subjects)

obese and non-obese combined

based on BMI (non-obese, obese) (n=74, 54)

B. Based on category of glucose tolerance at Year 1 (viz IGT_1 $Diabetes_1$ $Normal_1$):

obese and non-obese combined

based on BMI (non-obese, obese)

I PLASMA INSULIN RESPONSE DURING OGTT

A. TOTAL STUDY GROUP

1. Obese and non-obese combined

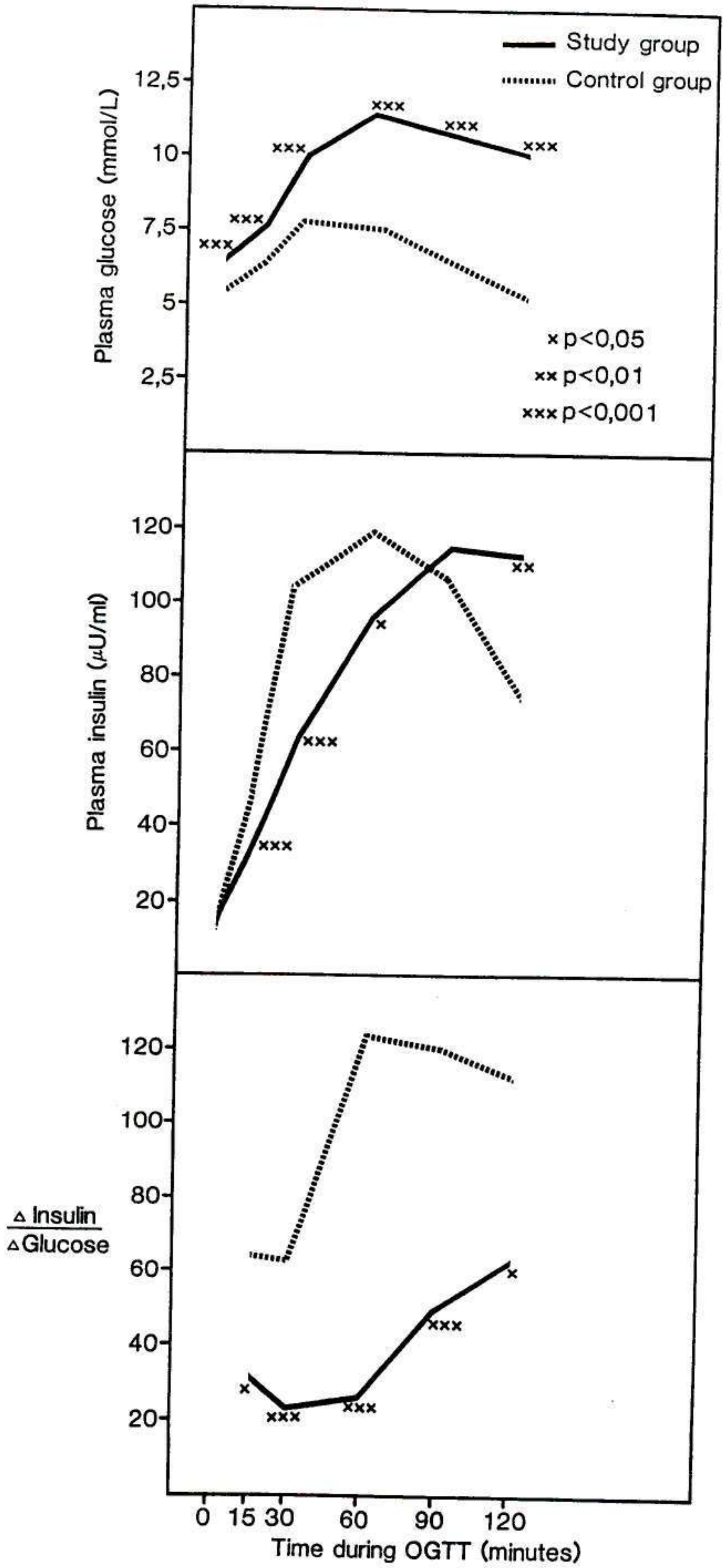
Table 1 : Figure 1

During OGTT, the mean plasma glucose levels as expected, were significantly higher in the study group compared to the control group, for each of the time intervals (p=0.0001 at 0, 15, 30, 60, 90 and 120 minutes).

Fasting plasma insulin levels were similar in the study group 14.3 ± 0.98 μu/ml and the control group 14.11 ± 1.5 μu/ml (p=0.45), whilst the 2 hour level was significantly higher in the study group 111.84 ± 7.85 μu/ml compared to the control group 74.01 ± 7.31 μu/ml (p=0.005).

At all other points during the OGTT except at 90 minutes, the Mean plasma insulin was significantly lower in the study group compared to the control group i.e. the study group, although having fasting plasma insulin levels similar to that of the control group, demonstrated a more delayed response during OGTT, with levels rising to a maximum at 90 minutes and higher than that of the control group. The control group on the other hand, demonstrated a brisk insulin response from baseline to a peak at 60 minutes, with a subsequent fall in plasma insulin levels.

Figure 1: Mean plasma glucose and insulin response, and Insulinogenic Index during OGTT at Year 1: total study group and control group.



Heterogeneity of insulin response is evident from the wide range and standard error for plasma insulin levels at each time interval (Table 1).

2. Based on BMI

Table 2, 3 ; Figure 2

a) In non-obese subjects, the mean plasma glucose was significantly higher in the study group compared to the control group, at all points during OGTT ($p=0.0001$ at 0, 15, 30, 60, 90 and 120 minutes). The mean fasting plasma insulin was higher in the study group, 13.16 ± 1.22 μu/ml, compared to the control group 10.60 ± 1.0 μu/ml; however the difference was not significant ($p=0.1$). Mean 2-hr plasma insulin was significantly higher in the study group 100.19 ± 8.82 μu/ml compared to the control group 67.85 ± 6.92 μu/ml ($p=0.005$). Compared to the control group, the study subjects demonstrated a delayed insulin response during OGTT, with peak levels at 90 and 120 minutes.

b) In obese subjects, mean plasma glucose was significantly higher in the study group compared to the control group, at all points during OGTT ($p=0.002$, 0.02, 0.001, 0.0001, 0.0001 at 0, 15, 30, 60, 90 and 120 minutes, respectively). Mean fasting plasma insulin was lower and mean 2-hr level was higher in the study group (15.87 ± 1.6 and 127.8 ± 13.96 μu/ml, respectively) compared to the control group (21.11 ± 3.6 and 86.03 ± 03 ± 16.86 μu/ml, respectively); however the difference was not significant. At 15, 30 and 60 minutes, plasma insulin was significantly lower in the study group ($p=0.003$, 0.005, 0.0167

Figure 2a

Figure 2b

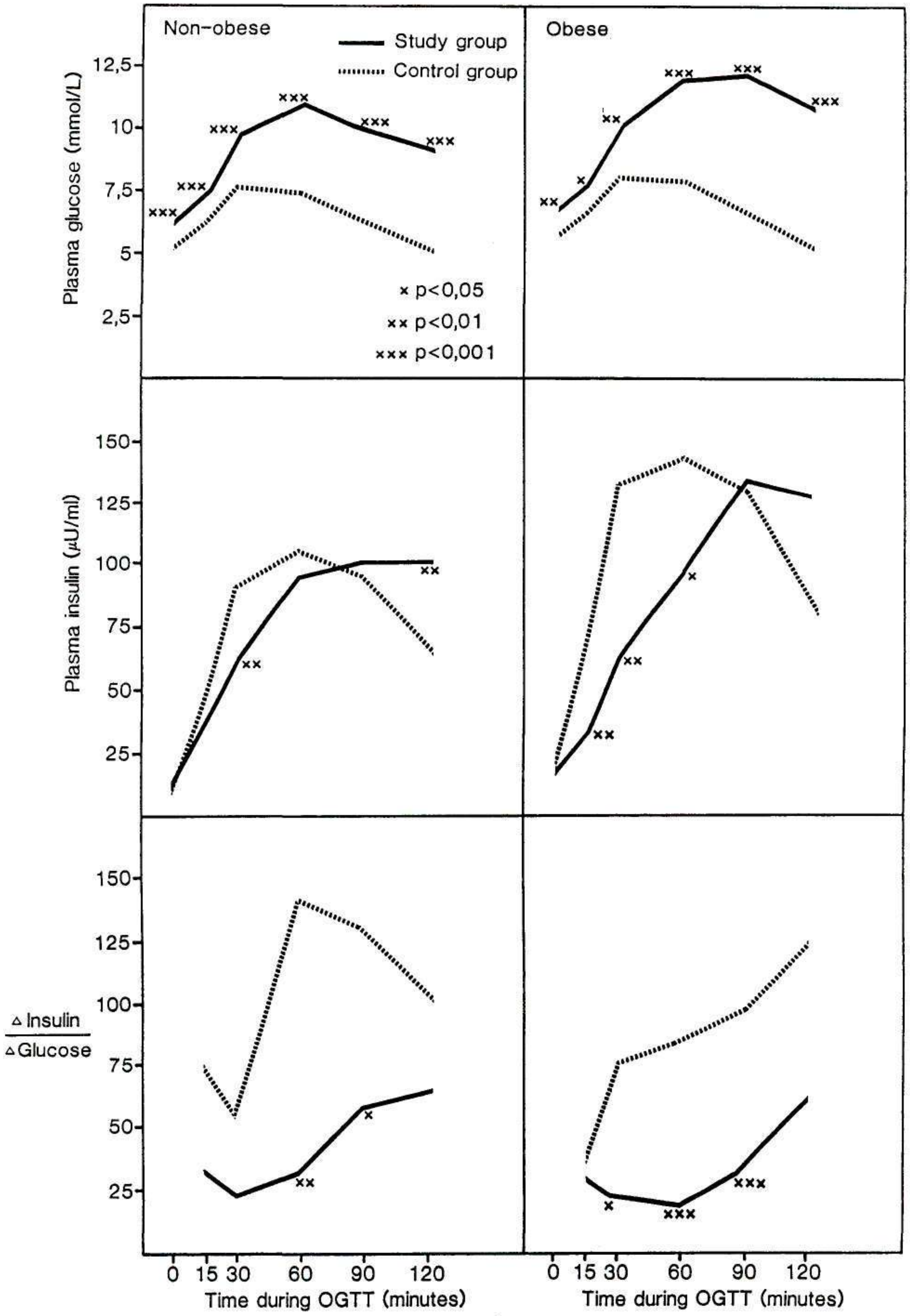


Figure 2a & 2b: Mean plasma glucose and insulin response, and Insulinogenic Index during OGTT at Year 1: total study group and control group based on BMI.

respectively) i.e. A pattern of delayed insulin response to glucose load was demonstrated in the study group.

c) In both the study group and control group, mean plasma glucose levels were higher in the obese subjects compared to the non-obese subjects, at each point during OGTT; however a significant difference was only noted for the study group at 90 and 120 minutes (p=0.002 and 0.03 respectively); and for the control group at 15 minutes (p=0.03).

As regards the insulin response in the control group, mean plasma insulin was higher in obese subjects compared to non-obese subjects at all points during OGTT, with a significant difference observed at 0, 15 and 60 minutes (p=0.01, 0.02 and 0.04, respectively). In the study group, although the mean plasma insulin was higher in the obese subjects at 0, 30, 90 and 120 minutes, no significant difference was observed between these and the non-obese subjects.

B. BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

1. Obese and non- obese combined

Table 4, 5, 6; Figure 3

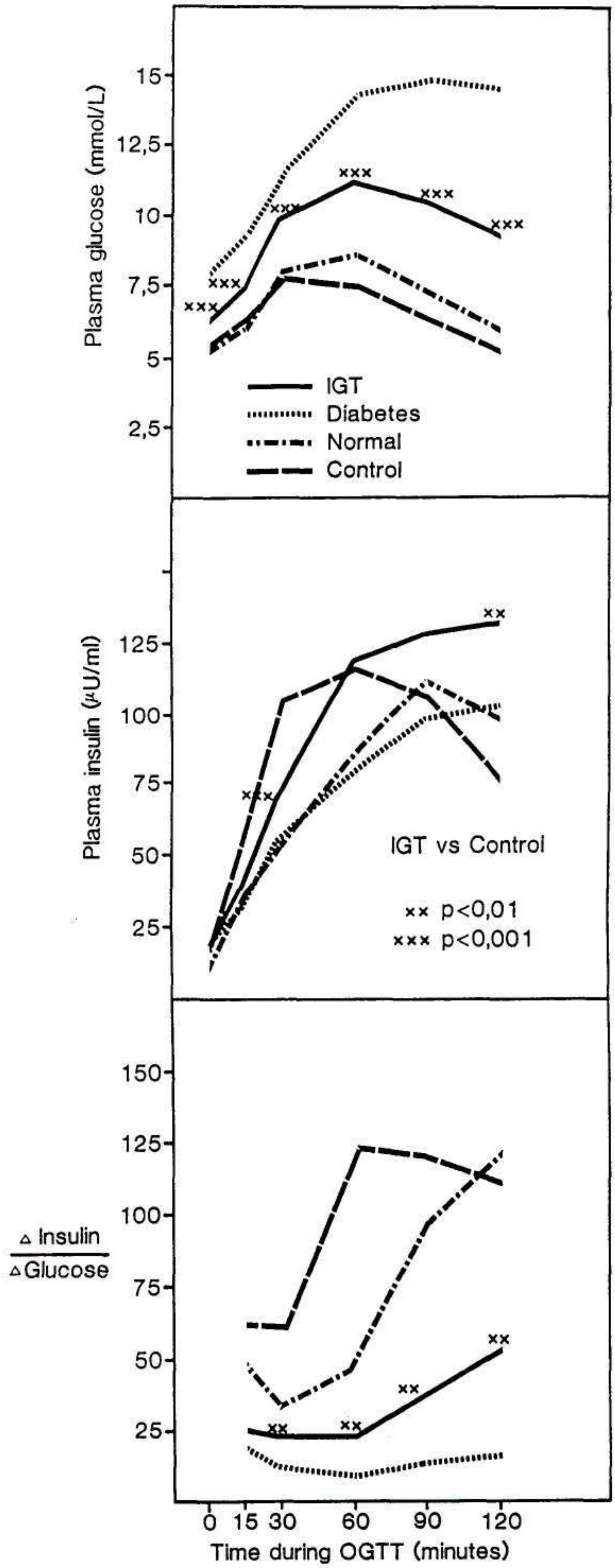
When the study group was divided according to the category of glucose tolerance at Year 1 ($Normal_1$ IGT_1 $Diabetes_1$), there was a significant difference in mean plasma glucose between each of the study groups at all points during OGTT i.e. the plasma glucose response of the 3 groups increased progressively from the $Normal_1$ group to the $Diabetes_1$ group (Table 6). The 4 group comparison ($Normal_1$, IGT_1, $Diabetes_1$ and control group) demonstrated that at each point during OGTT, the mean plasma glucose was significantly lower in the control group compared to the IGT_1 and $Diabetes_1$ groups, respectively (p=0.0001) (Table 4 and 5). When the control group was compared to the $Normal_1$ group, mean plasma glucose was similar at all points during OGTT except at 60 minutes, when the level was significantly higher in the $Normal_1$ group (Table 4 and 5, Figure 3).

From Table 4 and 5 and Figure 3, it is obvious that the relationship between the 4 categories of glucose tolerance and the insulin response is complicated, thus defying simple description and comparison.

Figure 3 demonstrates that except for the fasting values, the plasma insulin response was higher in the IGT_1 group compared to the $Diabetes_1$ and $Normal_1$ groups (i.e. hyperinsulinaemia in the IGT_1 group); when compared to the control group, the levels were higher at 0, 90 and 120 minutes in the IGT_1 group. Of note, in addition, is that the fasting and 2-hr insulin levels were higher in the $Diabetes_1$ group compared to the control group and $Normal_1$ group.

Table 4 and 5 demonstrates the comparison between the 4 groups by analysis of variance (ANOVA) - there was a significant interaction between thegroups at 15, 30, 60 and 120 minutes (p=0.0001, 0.0001, 0.0093, 0.0056, respectively). Whilst the overall interaction between the 4 groups was not significant at 0 minutes (p=0.08), of note is that the mean fasting (0 min) plasma insulin was highest in the $Diabetes_1$ groups (16.36 μu/ml) with progressively decreasing levels

Figure 3: Mean plasma glucose and insulin response, and Insulinogenic Index during OGTT at Year 1: based on category of glucose tolerance.



for the remaining 3 groups (16.09 μu/ml, 14.11 μu/ml and 10.10 μu/ml for the IGT_1 control and $Normal_1$ groups respectively).

At 120 minutes (2 hrs), mean plasma insulin response was highest in the IGT_1 group 132 ± 12.3 μu/ml, with progressively lower levels in the remaining 3 groups (103.3 μu/ml, 96.86 μu/ml, and 74.01 μu/ml in the $Diabetes_1$ $Normal_1$ and control group, respectively). At this time interval, mean plasma insulin was significantly higher in the IGT_1 group compared to the control group and $Normal_1$ group, employing Duncan's Multiple Range Test.

Thus, fasting (0 min) and 2 hr (120 min) plasma insulin levels were higher in the IGT_1 and $Diabetes_1$ groups, compared to the control group i.e. the IGT_1 and $Diabetes_1$ groups demonstrated both fasting and 2 hr hyperinsulinaemia.

Plasma insulin responses at the other time intervals during OGTT are illustrated and tabulated in Figure 3 and Tables 4-6.

Of importance, is the demonstration of different patterns of plasma insulin response during OGTT in the control group compared to the study groups. In the control group, in response to the oral glucose load, there was a prompt and brisk increase in plasma insulin level to a peak at 60 minutes, followed by decreasing levels in concert with the fall in the plasma glucose levels. This was in contrast to the finding in the IGT_1 and $Diabetes_1$ groups, in which, although fasting plasma insulin levels were higher, the response to the glucose load was more delayed and insulin levels progressively increased with the duration of the OGTT, maximum levels being achieved only at 120 minutes (despite the falling levels of plasma glucose, albeit small).

2. <u>Based on BMI</u>

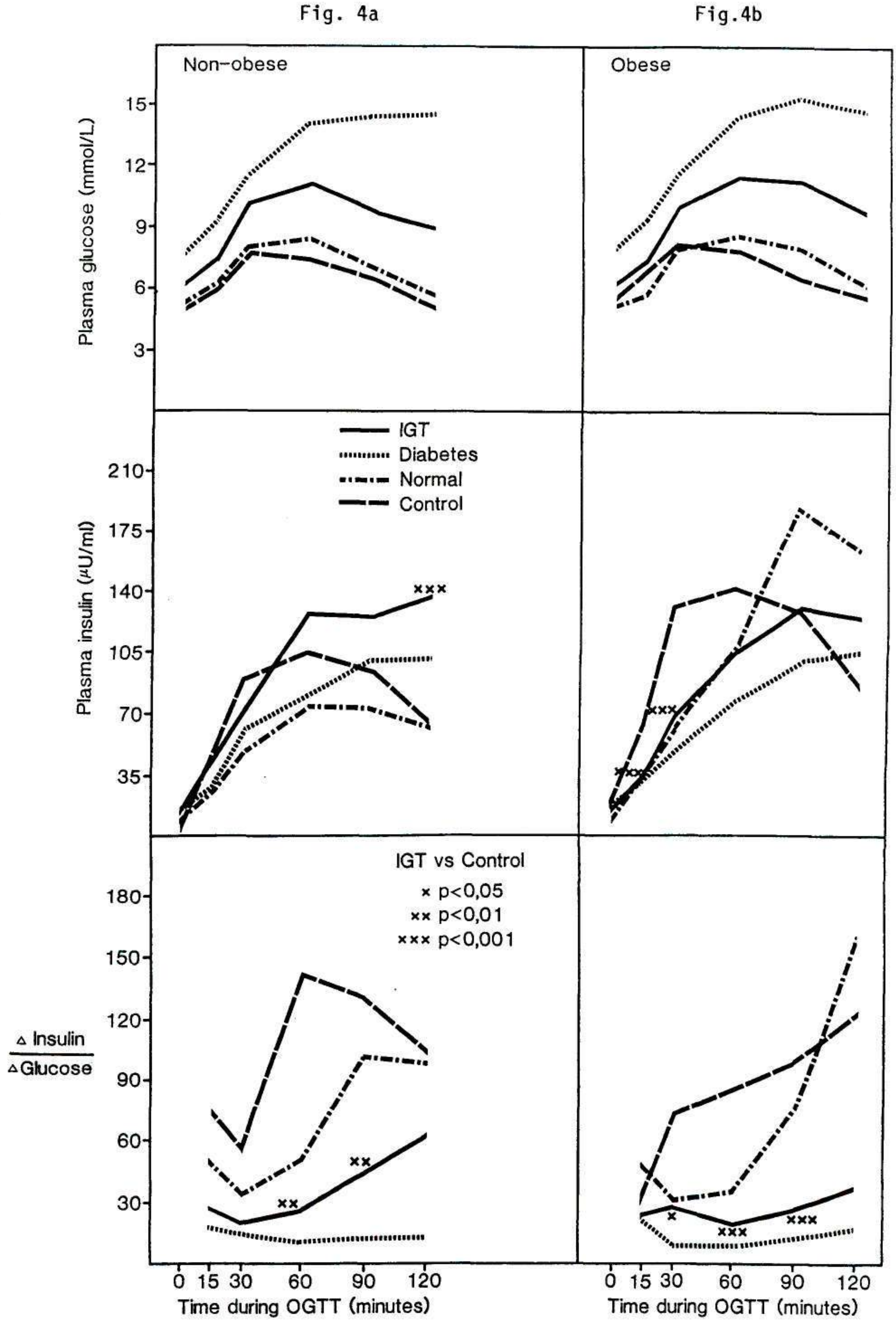
Table 7 - 10, Figure 4

a) In non-obese subjects, during OGTT, the plasma glucose response of the 4 groups increased progressively from the control group to the $Diabetes_1$ group [$Control_1$ ⟶ $Normal_1$ ⟶ IGT_1 ⟶ $Diabetes_1$], with a significant interaction between the 4 groups (p=0.0001) (Table 7) . Using Duncan's Multiple Range Test, it was found that the mean plasma glucose level, for any given time point during OGTT, was significantly different for each of the 3 study groups (IGT_1 $Diabetes_1$ $Normal_1$), but that the levels in the $Normal_1$ and control groups were similar; when compared to each of the remaining study groups (IGT_1 and $Diabetes_1$), the mean plasma glucose was significantly lower in the control group.

As regards plasma insulin response, Figure 4 demonstrates that the IGT_1 group exhibited higher mean plasma insulin (hyperinsulinaemia) for all points during OGTT when compared tothe remaining 2 study groups ($Diabetes_1$ $Normal_1$); and for all points, except at 30 minutes, when compared to the control group. What is also apparent is that the plasma insulin response of the 3 study groups decreased progressively from the IGT_1 group ⟶ $Diabetes_1$ group ⟶ $Normal_1$ group.

Comparison between the 4 groups by ANOVA showed that there was

Figure 4a & 4b: Mean plasma glucose and insulin response, and Insulinogenic Index during OGTT at Year 1: based on category of glucose tolerance and BMI.



significant interaction at 0, 30, 60, 90 and 120 minutes (p=0.008, p=0.01, p=0.027, p=0.047, p=0.0001, respectively). Although mean fasting plasma insulin was higher in the IGT_1 group (15.68μu/ml) compared to the control group (10.60 μu/ml), the difference was not significant; mean 2-hr (120 minutes) plasma insulin was significantly higher in the IGT_1 group (135.92 μu/ml) compared to the control group (67.85 μu/ml), $Diabetes_1$ group (101.19 μu/ml) and $Normal_1$ group (63.73 μu/ml).

b) In obese subjects, the plasma glucose response showed similar trends in all 4 groups, as in non-obese subjects. Of note, was the finding that at 15 minutes, obese control subjects had mean plasma glucose levels which were higher than $Normal_1$ group and similar to those of IGT_1 group (Table 8, Figure 4).

Plasma insulin response during OGTT in obese subjects was somewhat different to that found in non-obese subjects. Comparison between the 4 groups revealed significant interactions at 15 minutes and 30 minutes only (p=0.007, p=0.0006, respectively). The mean fasting (0 minute) plasma insulin was lower and mean 2-hr (120 minutes) level higher in the IGT_1 group compared to the control group; however the difference was not significant (16.66 vs 21.11 μu/ml at 0 minute; 126.73 vs 86.03 μu/ml at 120 minutes). Mean fasting plasma insulin was highest in the control group and lowest in the $Normal_1$ group; however no significant difference was observed between the 4 groups. At 120 minutes, the levels were highest in the $Normal_1$ group with progressively decreasing levels in the IGT_1 $Diabetes_1$ and control groups.

c) For each of the 4 sub-groups, comparison between obese and non-obese subjects was undertaken with respect to each of the variables viz. plasma insulin and plasma glucose (Table 10). In the IGT_1 and $Diabetes_1$ groups, no significant difference was observed between obese and non-obese subjects for mean plasma insulin response (at each of the time intervals during OGTT); in the $Normal_1$ group, obese subjects had significantly higher mean plasma insulin at 120 minutes (p=0.016), whilst in the control group, obese subjects had significantly higher mean plasma insulin at 0, 15 and 60 minutes (p=0.01, p=0.02, p=0.04, respectively).

In the $Diabetes_1$ and $Normal_1$ groups, mean plasma glucose was similar in obese and non-obese subjects for each of the time points during OGTT; in the IGT_1 group, mean plasma glucose was significantly higher in obese subjects at 90 minutes and 120 minutes (p=0.008, p=0.02, respectively); in the control group obese subjects demonstrated a significantly higher level at 15 minutes (p=0.03).

II INSULINOGENIC INDEX ($\frac{\Delta \text{ INSULIN}}{\Delta \text{ GLUCOSE}}$; INSULIN : GLUCOSE RATIO)

Results summarised in Table 1-11, Figure 1-4

A. TOTAL STUDY GROUP

1. Obese and non-obese combined

Table 1, Figure 1

The Mean Insulinogenic Index was strikingly attenuated in the study group compared to the control group, and a significant difference was observed between the two groups at all time points during OGTT, except at 15 minutes (p=0.0004, p=0.0001, p=0.0003, p=0.01 at 30, 60, 90 and 120 minutes, respectively). This was so, despite the higher plasma insulin response in the study group compared to the control group at 0 minute, 90 minutes and 120 minutes.

2. Based on BMI:

Table 2 and 3, Figure 2

a) In non-obese subjects, the Mean Insulinogenic Index was lower in the study group compared to the control group for all time points during OGTT, a significant difference being observed at 60 minutes and 90 minutes (p=0.008, p=0.02, respectively).

b) The attenuated response in the study group compared to the control group was also observed in obese subjects in whom the Mean Insulinogenic Index was significantly lower in the study group at 30 minutes, 60 minutes and 90 minutes ($p=0.044$, $p=0.0008$, $p=0.0000$, respectively).

c) In both the study group and control groups, no significant difference was demonstrated in Mean Insulinogenic Index, between obese and non-obese subjects.

B. BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

1. Obese and non-obese combined:

Table 4-6, Figure 3

Figure 3 demonstrates effectively that the Mean Insulinogenic Index was highest in the control group for all time intervals during OGTT except at 120 minutes, with progressively decreasing levels in the remaining 3 groups ($Normal_1 \rightarrow IGT_1 \rightarrow Diabetes_1$); the $Diabetes_1$ group exhibited the lowest levels. This was so despite the fact that the IGT_1 group and $Diabetes_1$ group demonstrated an apparent adequate plasma insulin response during OGTT, and in the case of the IGT_1 group, higher plasma insulin levels compared to the control group at 60, 90 and 120 minutes. Of note, was the finding that even in the $Normal_1$ group, the Mean Insulinogenic Index was lower than that in the control group at all points during OGTT except at 120 minutes (despite plasma glucose levels being similar in these two groups).

Comparison between the 4 groups by ANOVA demonstrated significant interaction at all time intervals during OGTT except at 15 minutes ($p=0.0029$, $p=0.0002$, $p=0.0001$ $p=0.0001$, at 30, 60, 90 and 120 minutes, respectively) (Table 5). When the IGT_1 group was compared to the control group, the Mean Insulinogenic Index was lower at all points during OGTT, a significant difference between the two groups being observed at 30, 60, 90 and 120 minutes. The Mean Insulinogenic Index was significantly lower in the $Diabetes_1$ group compared to the control group, for each time point of the OGTT. When the $Normal_1$ group was compared to the control group, the levels were lower at all time points except at 120 minutes; however a significant difference between the two groups was only observed at 60 minutes. At 15 minutes, the Mean Insulinogenic Index was lowest in the $Diabetes_1$ group (19.82), with progressively increasing levels in the remaining three groups (25.98, 49.22, 62.77 for IGT_1 $Normal_1$ and control group, respectively), with a significant difference between the $Diabetes_1$ group and control group at this time point. At 120 minutes, the level was lowest in the $Diabetes_1$ group (16.06) with a progressive increase in the remaining three groups (53.3, 111.09, 118.72 for IGT_1, Control and $Normal_1$ groups, respectively); at this time point, there was a significant difference in Mean Insulinogenic Index between the $Diabetes_1$ group compared to the $Normal_1$ group and control group, respectively, and between the IGT_1 compared to the $Normal_1$ group and control group respectively.

2. <u>Based on BMI</u>:

Tables 7, 8, 9, 11, Figure 4

a) In non-obese subjects, for the duration of the OGTT, the Mean Insulinogenic Index was highest in the control group, lowest in the $Diabetes_1$ group, with the responses in the $Normal_1$ group and IGT_1

group being intermediate ($Control_1$ ⟶ $Normal_1$ ⟶ IGT_1 ⟶ $Diabetes_1$). This was so, despite the plasma insulin response being higher in the $Diabetes_1$ group and IGT_1 group, compared certainly to those in the $Normal_1$ group, and for many time points when compared to the control group (Figure 4). Intergroup comparison demonstrated significant interaction at 60, 90 and 120 minutes (p=0.004, p=0.008, p=0.017, respectively) (Table 7). When compared to the control group, the Mean Insulinogenic Index was significantly lower in the IGT_1 group at 60 and 90 minutes; a significant difference was observed between the $Diabetes_1$ group and control group at 60, 90 and 120 minutes.

b) In obese subjects, a similar trend was observed (i.e. highest levels in the control group and lowest levels in the $Diabetes_1$ group), with the exception that at 15 minutes and 120 minutes, the Mean Insulinogenic Index was highest in the $Normal_1$ group (Figure 4). Intergroup comparison revealed a significant interaction at all time points during OGTT (p=0.037, p=0.018, p=0.0001, p=0.0001, p=0.007 at 15, 30, 60, 90 and 120 minutes, respectively) (Table 8). When compared to the control group,the Mean Insulinogenic Index was significantly lower in IGT_1 group at 30, 60 and 90 minutes; a significant difference between the $Diabetes_1$ and Control group was observed at all points, except at 15 minutes.

c) For each of the 4 groups (IGT_1, $Normal_1$, $Diabetes_1$, Control), no signficant difference was observed in Mean Insulinogenic Index, between obese and non-obese subjects for any of the time points during OGTT (Table 11).

Table 1

PLASMA INSULIN RESPONSE AND INSULINOGENIC INDEX DURING OGTT AT YEAR 1: STUDY GROUP AND CONTROL GROUP

TIME DURING OGTT (min)	STUDY GROUP (n=128)	CONTROL GROUP (n=60)	P
	*PLASMA GLUCOSE (mmol/L)		
0 min	6.49 ± 0.14 (3.4-11.6)	5.43 ± 0.11 (3.4- 7.7)	0.0001
15 min	7.64 ± 0.18 (3.8-15.5)	6.39 ± 0.14 (4.7-10.0)	0.0001
30 min	9.85 ± 0.20 (4.0-16.7)	7.79 ± 0.21 (4.3-14.8)	0.0001
60 min	11.32 ± 0.28 (4.2-19.4)	7.52 ± 0.29 (4.1-15.4)	0.0001
90 min	10.86 ± 0.34 (2.9-22.9)	6.39 ± 0.21 (3.1-11.5)	0.0001
120 min	10.01 ± 0.36 (2.4-23.7)	5.23 ± 0.16 (2.7- 7.5)	0.0001
	*PLASMA INSULIN (μu/ml)		
0 min	14.30 ± 0.98 (1.5- 52.5)	14.11 ± 1.50 (1.0- 56.4)	ns
15 min	34.91 ± 2.15 (3.1-105.7)	51.95 ± 4.77 (4.6-152.5)	0.0001
30 min	61.15 ± 4.12 (3.7-253.2)	104.65 ± 9.71 (27.5-470.0)	0.0001
60 min	95.48 ± 6.76 (3.7-409.4)	118.12 ± 8.27 (17.9-315.7)	0.0167
90 min	113.63 ± 9.32 (3.4-759.7)	106.60 ± 8.90 (15.3-321.6)	ns
120 min	111.84 ± 7.85 (5.7-484.4)	74.01 ± 7.31 (15.3-298.6)	0.005
	*INSULINOGENIC INDEX $\left(\frac{\Delta \text{ INSULIN}}{\Delta \text{ GLUCOSE}}\right)$		
15 min	31.27 ± 5.74 (0.31-664.0)	62.77 ± 16.49 (0.67-943.0)	ns
30 min	23.33 ± 4.90 (0.23-550.5)	62.19 ± 12.46 (4.98-493.67)	0.0004
60 min	26.78 ± 4.67 (0.31-524.0)	123.42 ± 26.63 (2.39-1203.0)	0.0001
90 min	47.75 ± 8.10 (0.18-692.0)	119.86 ± 19.44 (15.46- 844.0)	0.0003
120 min	61.82 ± 10.32 (0.20-996.6)	111.09 ± 17.73 (1.57- 676.0)	0.01

*Mean ± SE (Range)

Table 2a

*PLASMA INSULIN RESPONSE AND INSULINOGENIC INDEX DURING OGTT AT YEAR 1
IN NON-OBESE STUDY GROUP AND CONTROL GROUP

TIME DURING OGTT (min)	STUDY GROUP (n=74)	CONTROL GROUP (n=40)	P
	PLASMA GLUCOSE (mmol/L)		
0 min	6.37 ± 0.17 (4.0-11.6)	5.32 ± 0.13 (3.4- 7.0)	0.0001
15 min	7.58 ± 0.23 (4.4-15.5)	6.19 ± 0.14 (4.7- 8.6)	0.0001
30 min	9.70 ± 0.26 (5.2-15.6)	7.66 ± 0.23 (4.3-10.5)	0.0001
60 min	10.91 ± 0.36 (4.3-17.7)	7.36 ± 0.33 (4.1-11.9)	0.0001
90 min	9.97 ± 0.42 (2.9-19.8)	6.30 ± 0.24 (3.1-10.3)	0.0001
120 min	9.34 ± 0.47 (2.4-22.7)	5.21 ± 0.20 (3.1- 7.5)	0.0001
	PLASMA INSULIN (μu/ml)		
0 min	13.16 ± 1.22 (1.5- 44.8)	10.60 ± 1.0 (1.0- 28.6)	ns
15 min	35.26 ± 3.04 (3.1-105.7)	44.05 ± 4.95 (4.6-147.8)	ns
30 min	61.03 ± 5.65 (3.7-253.2)	90.98 ± 9.21 (27.5-287.6)	0.004
60 min	95.58 ± 9.17 (3.7-409.4)	106.11 ± 9.13 (17.9-273.2)	ns
90 min	100.17 ± 8.61 (3.4-320.9)	95.08 ± 10.07 (15.3-278.7)	ns
120 min	100.19 ± 8.82 (5.7-421.9)	67.85 ± 6.92 (15.3-232.2)	0.005
	INSULINOGENIC INDEX $\left(\frac{\Delta \text{ INSULIN}}{\Delta \text{ GLUCOSE}}\right)$		
15 min	32.80 ± 9.39 (0.31-664.0)	74.58 ± 24.52 (0.67- 943.0)	ns
30 min	23.97 ± 7.58 (0.23-550.5)	55.99 ± 14.58 (4.98- 493.0)	0.056
60 min	32.06 ± 7.78 (0.31-524.0)	142.32 ± 38.93 (2.39-1203.0)	0.008
90 min	58.09 ± 13.0 (0.18-692.0)	130.58 ± 28.09 (15.46- 844.0)	0.02
120 min	63.51 ± 11.53 (0.34-507.85)	104.83 ± 20.71 (3.95- 676.0)	ns

*Mean ± SE (Range)

Table 2b

*PLASMA INSULIN RESPONSE AND INSULINOGENIC INDEX DURING OGTT AT YEAR 1: STUDY GROUP AND CONTROL GROUP – OBESE SUBJECTS

TIME DURING OGTT (min)	STUDY GROUP (n=54)	CONTROL GROUP (n=20)	p
	PLASMA GLUCOSE (mmol/L)		
0 min	6.68 ± 0.23 (3. 4-11.3)	5.64 ± 0.23 (4.7 - 7.7)	0.002
15 min	7.73 ± 0.29 (3. 8-15.1)	6.81 ± 0.28 (5.1 - 10.1)	0.02
30 min	10.06 ± 0.32 (4. 0-16.7)	8.04 ± 0.45 (5.4 - 14.8)	0.001
60 min	11.89 ± 0.42 (4. 2-19.4)	7.86 ± 0.57 (4.6 - 15.4)	0.0000
90 min	12.08 ± 0.52 (3. 9-22.9)	6.57 ± 0.42 (4.5 - 11.5)	0.0001
120 min	10.92 ± 0.55 (4. 0-23.7)	5.26 ± 0.26 (2.7 - 7.2)	0.0001
	PLASMA INSULIN (μu/ml)		
0 min	15.87 ± 1.59 (2. 3- 52.5)	21.11 ± 3.6 (4.5 - 56.4)	ns
15 min	34.43 ± 2.97 (3. 6- 91.0)	67.74 ± 9.56 (13.5 -152.5)	0.003
30 min	61.31 ± 5.99 (6. 0-226.7)	131.99 ± 21.72 (36.3 -470.0)	0.0048
60 min	95.35 ± 10.04 (7. 7-369.5)	142.15 ± 15.8 (69.4 -315.7)	0.0167
90 min	132.08 ± 18.51 (8. 0-759.7)	129.65 ± 16.71 (49.4 -321.6)	ns
120 min	127.80 ± 13.96 (10. 1-484.4)	86.03 ± 16.86 (22.6 -298.6)	ns
	INSULINOGENIC INDEX $\left(\frac{\Delta \text{ INSULIN}}{\Delta \text{ GLUCOSE}}\right)$		
15 min	29.17 ± 4.53 (0.32-141.0)	39.15 ± 4.60 (14.32- 85.93)	ns
30 min	22.45 ± 5.26 (0.52-265.0)	74.59 ± 23.69 (10.0 -493.67)	0.044
60 min	19.53 ± 2.80 (1.32-105.6)	85.61 ± 16.47 (16.06-280.0)	0.0008
90 min	33.59 ± 6.83 (1.66-250.3)	98.42 ± 15.66 (24.32-329.3)	0.0000
120 min	59.50 ± 18.81 (0.20-996.6)	123.61 ± 33.99 (1.57-607.43)	ns

* Mean ± SE (Range)

OBESITY : BMI ≥ 27 in males

≥ 25 in males

Table 3

MEAN PLASMA INSULIN RESPONSE AND INSULINOGENIC INDEX DURING OGTT AT YEAR 1: NON-OBESE vs OBESE SUBJECTS IN STUDY GROUP

*CATEGORY BASED ON BMI (n)	TIME DURING OGTT (MINUTES) 0	15	30	60	90	120
	MEAN PLASMA GLUCOSE (mmol/L)					
NON OBESE (74)	6.37	7.58	9.70	10.91	9.97	9.34
OBESE (54)	6.68	7.73	10.06	11.89	12.08	10.92
P	ns	ns	ns	ns	0.002	0.031
	MEAN PLASMA INSULIN (μu/ml)					
NON OBESE (74)	13.16	35.26	61.03	95.58	100.17	100.19
OBESE (54)	15.87	34.43	61.31	95.35	132.08	127.80
P	ns	ns	ns	ns	ns	ns
	MEAN INSULINOGENIC INDEX $\left(\frac{\Delta \text{ INSULIN}}{\Delta \text{ GLUCOSE}}\right)$					
NON OBESE (74)		32.80	23.97	32.06	58.09	63.51
OBESE (54)		29.17	22.45	19.53	33.59	59.50
P		ns	ns	ns	ns	ns

*Mean ± SE (Range)

OBESITY: BMI ≥ 27 in males

≥ 25 in females

Table 4

*PLASMA INSULIN RESPONSE AND INSULINOGENIC INDEX DURING OGTT AT YEAR 1: STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE, AND CONTROL GROUP

TIME DURING OGTT (min)	CATEGORY OF GLUCOSE TOLERANCE: IGT_1 (n=47)	$DIABETES_1$ (n=41)	$NORMAL_1$ (n=40)	CONTROL (n=60)
	PLASMA GLUCOSE (mmol/L)			
0 min	6.30 ± 0.12 (4.5 - 7.7)	7.88 ± 0.25 (5.5 - 11.6)	5.32 ± 0.15 (3.4 - 7.7)	5.43 ± 0.11 (3.4 - 7.7)
15 min	7.48 ± 0.16 (4.3 - 9.8)	9.34 ± 0.34 (5.5 - 15.5)	6.09 ± 0.20 (3.8 - 9.8)	6.39 ± 0.14 (4.7 - 10.0)
30 min	10.02 ± 0.23 (6.7 - 13.4)	11.44 ± 0.32 (8.0 - 16.7)	8.04 ± 0.30 (4.0 - 12.3)	7.79 ± 0.21 (4.3 - 14.8)
60 min	11.17 ± 0.28 (7.2 - 16.3)	14.33 ± 0.30 (11.1 - 19.4)	8.43 ± 0.36 (4.2 - 14.2)	7.52 ± 0.29 (4.1 - 15.4)
90 min	10.47 ± 0.27 (7.3 - 16.3)	14.93 ± 0.45 (10.1 - 22.9)	7.14 ± 0.31 (2.9 - 10.9)	6.39 ± 0.21 (3.1 - 11.5)
120 min	9.37 ± 0.15 (7.8 - 11.0)	14.69 ± 0.52 (11.1 - 23.7)	5.97 ± 0.20 (2.4 - 7.6)	5.23 ± 0.16 (2.7 - 7.5)
	PLASMA INSULIN (μu/ml)			
0 min	16.09 ± 1.66 (2.3 - 52.5)	16.36 ± 1.62 (1.9 - 48.3)	10.10 ± 1.63 (1.5 - 44.8)	14.11 ± 1.50 (1.0 - 56.4)
15 min	40.68 ± 3.8 (5.1 - 98.8)	31.32 ± 3.35 (3.1 - 91.0)	31.83 ± 3.85 (3.6 -105.7)	51.95 ± 4.77 (4.6 -152.5)
30 min	72.36 ± 7.55 (17.3 -226.7)	55.41 ± 7.48 (3.7 -253.2)	53.85 ± 5.72 (5.0 -126.8)	104.65 ± 9.71 (27.5 -470.0)
60 min	118.30 ± 13.49 (27.2 -409.4)	78.82 ± 8.96 (3.7 -237.4)	85.75 ± 10.7 (7.7 -369.5)	118.12 ± 8.27 (17.9 -315.7)
90 min	129.03 ± 12.7 (27.2 -320.9)	98.31 ± 13.37 (3.4 -459.1)	111.25 ± 21.9 (8.0 -759.7)	106.60 ± 8.90 (15.3 -321.6)
120 min	132.0 ± 12.3 (20.3 -421.9)	103.34 ± 13.88 (5.7 -484.4)	96.86 ± 14.53 (10.1 -450.7)	74.01 ± 7.31 (15.3 -298.6)
	INSULINOGENIC INDEX ($\frac{\Delta\ INSULIN}{\Delta\ GLUCOSE}$)			
15 min	25.98 ± 3.6 (0.39- 91.14)	19.82 ± 5.7 (0.31-202.5)	49.22 ± 16.69 (0.4 -664.0)	62.77 ± 16.49 (0.67- 943.0)
30 min	24.13 ± 6.2 (0.94-265.0)	12.52 ± 1.81 (0.45- 41.71)	33.47 ± 13.68 (0.23-550.5)	62.19 ± 12.46 (4.98- 493.67)
60 min	23.98 ± 3.84 (2.0 -135.67)	10.25 ± 1.47 (0.31- 39.3)	46.99 ± 13.65 (1.32-524.0)	123.42 ± 26.63 (2.39-1203.0)
90 min	37.85 ± 8.27 (2.3 -385.7)	13.65 ± 2.44 (0.18- 74.22)	94.35 ± 22.2 (1.70-692.0)	119.86 ± 19.44 (15.46- 844.0)
120 min	53.30 ± 10.98 (1.98-507.85)	16.06 ± 3.13 (0.2 - 94.53)	118.72 ± 28.14 (3.10-996.6)	111.09 ± 17.73 (1.57- 676.0)

* Mean ± SE (Range)

Table 5

MEAN PLASMA INSULIN, GLUCOSE, AND INSULINOGENIC INDEX DURING OGTT AT YEAR 1: STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE AND CONTROL GROUP

OGTT TIME (min)	CATEGORY OF GLUCOSE TOLERANCE				*p
	IGT_1 (n=47)	$DIABETES_1$ (n=41)	$NORMAL_1$ (n=40)	CONTROL (n=60)	
	MEAN PLASMA GLUCOSE (mmol/L)				
0	6.30^A	7.88^B	5.32^C	5.43^C	0.0001
15	7.48^A	9.34^B	6.09^C	6.39^C	0.0001
30	10.02^A	11.44^B	8.04^C	7.79^C	0.0001
60	11.17^A	14.33^B	8.43^C	7.52^D	0.0001
90	10.47^A	14.93^B	7.14^C	6.39^C	0.0001
120	9.37^A	14.69^B	5.95^C	5.23^C	0.0001
	MEAN PLASMA INSULIN (μu/ml)				
0	16.09^A	16.36^A	10.10^B	14.11^{A,B}	0.08
15	40.68^{A,B}	31.32^B	31.83^B	51.95^A	0.0001
30	72.36^B	55.41^B	53.85^B	104.65^A	0.0001
60	118.30^A	78.82^B	85.75^B	118.12^A	0.0093
90	129.03	98.31	111.25	106.60	ns
120	132.00^A	103.34^{A,B}	96.86^B	74.01^B	0.0056
	INSULINOGENIC INDEX $\left(\frac{\Delta\ \text{INSULIN}}{\Delta\ \text{GLUCOSE}}\right)$				
15	25.98^{A,B}	19.82^B	49.22^{A,B}	62.77^A	ns
30	24.13^B	12.52^B	33.47^{A,B}	62.19^A	0.0029
60	23.98^B	10.25^B	46.99^B	123.42^A	0.0002
90	37.85^B	13.65^B	94.35^A	119.86^A	0.0001
120	53.30^B	16.06^B	118.72^A	111.09^A	0.0001

*p values are for comparisons between the four groups by analysis of variance

A,B,C,D: Mean values with the same letter are not significantly different.

Table 6

MEAN PLASMA INSULIN RESPONSE AND INSULINOGENIC INDEX AT YEAR 1: STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE

OGTT TIME (min)	CATEGORY OF GLUCOSE TOLERANCE			*p
	IGT_1 (n=47)	$DIABETES_1$ (n=41)	$NORMAL_1$ (n=40)	
	PLASMA GLUCOSE (mmol/L)			
0	6.30^{A}	7.88^{B}	5.32^{C}	0.0001
15	7.48^{A}	9.34^{B}	6.09^{C}	0.0001
30	10.02^{A}	11.44^{B}	8.04^{C}	0.0001
60	11.17^{A}	14.33^{B}	8.43^{C}	0.0001
90	10.47^{A}	14.93^{B}	7.14^{C}	0.0001
120	9.37^{A}	14.69^{B}	5.95^{C}	0.0001
	PLASMA INSULIN (μu/ml)			
0	16.09^{A}	16.36^{A}	10.10^{B}	0.008
15	40.68	31.32	31.83	ns
30	72.36	55.41	53.85	ns
60	118.30^{A}	$78.82^{A,B}$	85.75^{A}	0.03
90	129.03	98.31	111.25	ns
120	132.00	103.34	96.86	ns
	INSULINOGENIC INDEX ($\frac{\Delta \text{ INSULIN}}{\Delta \text{ GLUCOSE}}$)			
15	$25.98^{A,B}$	19.82^{B}	49.22^{A}	ns
30	24.13	12.52	33.47	ns
60	23.98^{A}	10.25^{A}	46.99^{B}	0.0095
90	37.85^{A}	13.65^{A}	94.35^{B}	0.0005
120	53.30^{A}	16.06^{A}	118.72^{B}	0.0007

*p values are for comparisons between the three groups by analysis of variance
A,B,C : Mean values with the same letter are not significantly different.

Table 7

MEAN PLASMA GLUCOSE, INSULIN AND INSULINOGENIC INDEX DURING OGTT AT YEAR 1: IN NON-OBESE SUBJECTS: STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE

OGTT TIME (min)	CATEGORY OF GLUCOSE TOLERANCE				*p
	IGT_1 (n=27)	$DIABETES_1$ (n=20)	$NORMAL_1$ (n=27)	CONTROL (n=40)	
	MEAN PLASMA GLUCOSE (mmol/L)				
0	6.32^{A}	7.82^{B}	5.33^{C}	5.32^{C}	0.0001
15	7.56^{A}	9.38^{B}	6.26^{C}	6.19^{C}	0.0001
30	10.13^{A}	11.37^{B}	8.04^{C}	7.66^{C}	0.0001
60	11.01^{A}	14.20^{B}	8.36^{C}	7.36^{C}	0.0001
90	9.87^{A}	14.43^{B}	6.76^{C}	6.30^{C}	0.0001
120	9.09^{A}	14.54^{B}	5.74^{C}	5.21^{C}	0.0001
	MEAN PLASMA INSULIN (μu/ml)				
0	15.68^{A}	15.67^{A}	8.78^{B}	$10.60^{A,B}$	0.008
15	44.17	30.08	30.19	44.05	ns
30	$73.67^{A,B}$	61.06^{B}	48.37^{B}	90.98^{A}	0.01
60	127.58^{A}	80.51^{B}	74.73^{B}	$106.11^{A,B}$	0.027
90	126.87^{A}	$99.71^{A,B}$	73.83^{B}	$95.08^{A,B}$	0.047
120	135.92^{A}	101.19^{B}	63.73^{C}	$67.85^{B,C}$	0.0001
	MEAN INSULINOGENIC INDEX $\left(\frac{\Delta \text{ INSULIN}}{\Delta \text{ GLUCOSE}}\right)$				
15	26.41	18.49	49.80	74.58	ns
30	20.73	14.17	34.47	56.00	ns
60	27.54^{B}	10.45^{B}	52.59^{B}	142.32^{A}	0.004
90	$45.84^{B,C}$	14.38^{C}	$102.72^{A,B}$	130.58^{A}	0.008
120	$65.02^{A,B}$	14.37^{B}	98.39^{A}	104.83^{A}	0.017

*p values are for comparisons between the four groups by analysis of variance

A,B,C : Mean values with the same letter are not significantly different

Table 8

MEAN PLASMA GLUCOSE, INSULIN AND INSULINOGENIC INDEX DURING OGTT AT YEAR 1: IN OBESE SUBJECTS: Study GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE

OGTT TIME (min)	CATEGORY OF GLUCOSE TOLERANCE				*p
	IGT_1 (n=20)	$DIABETES_1$ (n=21)	$NORMAL_1$ (n=13)	CONTROL (n=20)	
	MEAN PLASMA GLUCOSE (mmol/L)				
0	6.28^{A}	7.94^{A}	5.28^{C}	5.64^{B,C}	0.0001
15	7.37^{B}	9.31^{A}	5.74^{C}	6.81^{B}	0.0001
30	9.86^{B}	11.50^{A}	8.02^{C}	8.04^{C}	0.0001
60	11.38^{B}	14.45^{A}	8.57^{C}	7.86^{C}	0.0001
90	11.27^{B}	15.41^{A}	7.93^{C}	6.57^{C}	0.0001
120	9.75^{B}	14.84^{A}	6.37^{C}	5.26^{C}	0.0001
	MEAN PLASMA INSULIN (μu/ml)				
0	16.66	17.01	12.83	21.11	ns
15	35.96^{B}	32.49^{B}	35.22^{B}	67.74^{A}	0.0007
30	70.60^{B}	50.02^{B}	65.25^{B}	132.0^{A}	0.0006
60	105.77^{A,B}	77.22^{B}	108.62^{A,B}	142.15^{A}	0.051
90	131.94	96.98	188.99	129.63	ns
120	126.73	105.40	165.66	86.03	ns
	MEAN INSULINOGENIC INDEX $\left(\frac{\Delta\ INSULIN}{\Delta\ GLUCOSE}\right)$				
15	25.40^{B}	21.09^{B}	48.02^{A}	39.15^{A,B}	0.037
30	28.71^{B}	10.95^{B}	31.38^{B}	74.59^{A}	0.018
60	19.18^{B}	10.06^{B}	35.39^{B}	85.61^{A}	0.0001
90	27.07^{B}	12.95^{B}	76.97^{A}	98.42^{A}	0.0001
120	37.49^{B,C}	17.67^{C}	106.95^{A}	123.61^{A,B}	0.007

*p values are for comparisons between the four groups by analysis of variance
A,B,C: Mean values with the same letter are not significantly different

Table 9

MEAN PLASMA GLUCOSE (mmol/L) DURING OGTT AT YEAR 1: NON-OBESE vs OBESE IN STUDY GROUPS AND CONTROL GROUP

*CATEGORY BASED ON BMI (n)	TIME DURING OGTT (MINUTES)					
	0	15	30	60	90	120
	MEAN PLASMA GLUCOSE (mmol/L)					
	IGT_1					
NON-OBESE (27)	6.32	7.56	10.13	11.01	9.87	9.09
OBESE (20)	6.28	7.37	9.86	11.38	11.27	9.75
p	–	–	–	–	0.008	0.02
	$DIABETES_1$					
NON-OBESE (20)	7.82	9.38	11.37	14.20	14.43	14.54
OBESE (21)	7.94	9.31	11.50	14.45	15.41	14.84
p	–	–	–	–	–	–
	$NORMAL_1$					
NON-OBESE (27)	5.33	6.26	8.04	8.36	6.76	5.74
OBESE (13)	5.28	5.74	8.02	8.57	7.93	6.37
	CONTROL					
NON-OBESE (40)	5.32	6.19	7.66	7.36	6.30	5.21
OBESE (20)	5.64	6.81	8.04	7.86	6.57	5.26
p	–	0.03	–	–	–	–

*OBESITY: BMI ≥ 27 in males
≥ 25 in females

–p not significant

Table 10

MEAN PLASMA INSULIN (μu/ml) DURING OGTT AT YEAR 1 : NON-OBESE vs OBESE, IN STUDY GROUPS AND CONTROL GROUP

*CATEGORY BASED ON BMI (n)	TIME DURING OGTT (MINUTES)					
	0	15	30	60	90	120
	MEAN PLASMA INSULIN (μu/ml)					
	IGT_1					
NON-OBESE (27)	15.68	44.17	73.67	127.58	126.87	135.92
OBESE (20)	16.66	35.96	70.60	105.77	131.94	126.73
p	–	–	–	–	–	–
	$DIABETES_1$					
NON-OBESE (20)	15.67	30.08	61.06	80.51	99.71	101.19
OBESE (21)	17.01	32.49	50.02	77.22	96.98	105.40
p	–	–	–	–	–	–
	$NORMAL_1$					
NON-OBESE (27)	8.78	30.19	48.37	74.73	73.83	63.73
OBESE (13)	12.83	35.22	65.25	108.62	188.99	165.66
p	–	–	–	–	–	0.016
	CONTROL					
NON-OBESE (40)	10.60	44.05	90.98	106.11	95.08	67.85
OBESE (20)	21.11	67.74	132.0	142.15	129.63	86.03
p	0.01	0.02	–	0.04	–	–

*OBESITY: BMI ≥ 27 in males
≥ 25 in females

–p not significant

Table 11

MEAN INSULINOGENIC INDEX $\left(\frac{\Delta \text{ INSULIN}}{\Delta \text{ GLUCOSE}}\right)$ DURING OGTT AT YEAR 1 : NON-OBESE vs OBESE IN STUDY GROUPS AND CONTROL GROUP

*CATEGORY BASED ON BMI (n)	TIME DURING OGTT (MINUTES)				
	15	30	60	90	120
	MEAN INSULINOGENIC INDEX				
	IGT_1				
NON-OBESE (27)	26.41	20.73	27.54	45.84	65.02
OBESE (20)	25.40	28.71	19.18	27.07	37.49
p	–	–	–	–	–
	$DIABETES_1$				
NON-OBESE (20)	18.49	14.17	10.45	14.38	14.37
OBESE (21)	21.09	10.95	10.06	12.95	17.67
p	–	–	–	–	–
	$NORMAL_1$				
NON-OBESE (27)	49.80	34.47	52.59	102.72	98.39
OBESE (13)	48.02	31.38	35.39	76.97	160.95
p	–	–	–	–	–
	CONTROL				
NON-OBESE (40)	74.58	56.0	142.32	130.58	104.83
OBESE (20)	39.15	74.59	85.61	98.42	123.61
p	–	–	–	–	–

*OBESITY: BMI ≥ 27 in males
≥ 25 in females

–p not significant

III INSULIN RATIOS

Results are summarised in Table 12-16, Figure 5-7

A. TOTAL STUDY GROUP

1. Obese and non-obese combined:

Table 12, Figure 5

The mean fasting insulin: glucose ratio was significantly lower in the study group 2.21 ± 0.16, compared to the control group 2.58 ± 0.27, p=0.03.

The mean 2-hr insulin: fasting insulin ratio was significantly higher in the study group 11.32 ± 1.23 compared to the control group 7.10 ± 0.88, p=0.02.

No significant difference was observed in mean 2-hr insulin: 2-hr glucose ratio between the study group (12.69 ± 0.098) and control group (12.74 ± 1.07)

2. Based on BMI

Table 13, Figure 5

a) In non-obese subjects, no significant difference was observed between the study group and control group, for each of the three ratios (fasting insulin : glucose ; 2-hr insulin : 2-hr glucose; 2-hr insulin : fasting insulin).

Figure 5: Insulin Ratios at Year 1: total study group and control group.

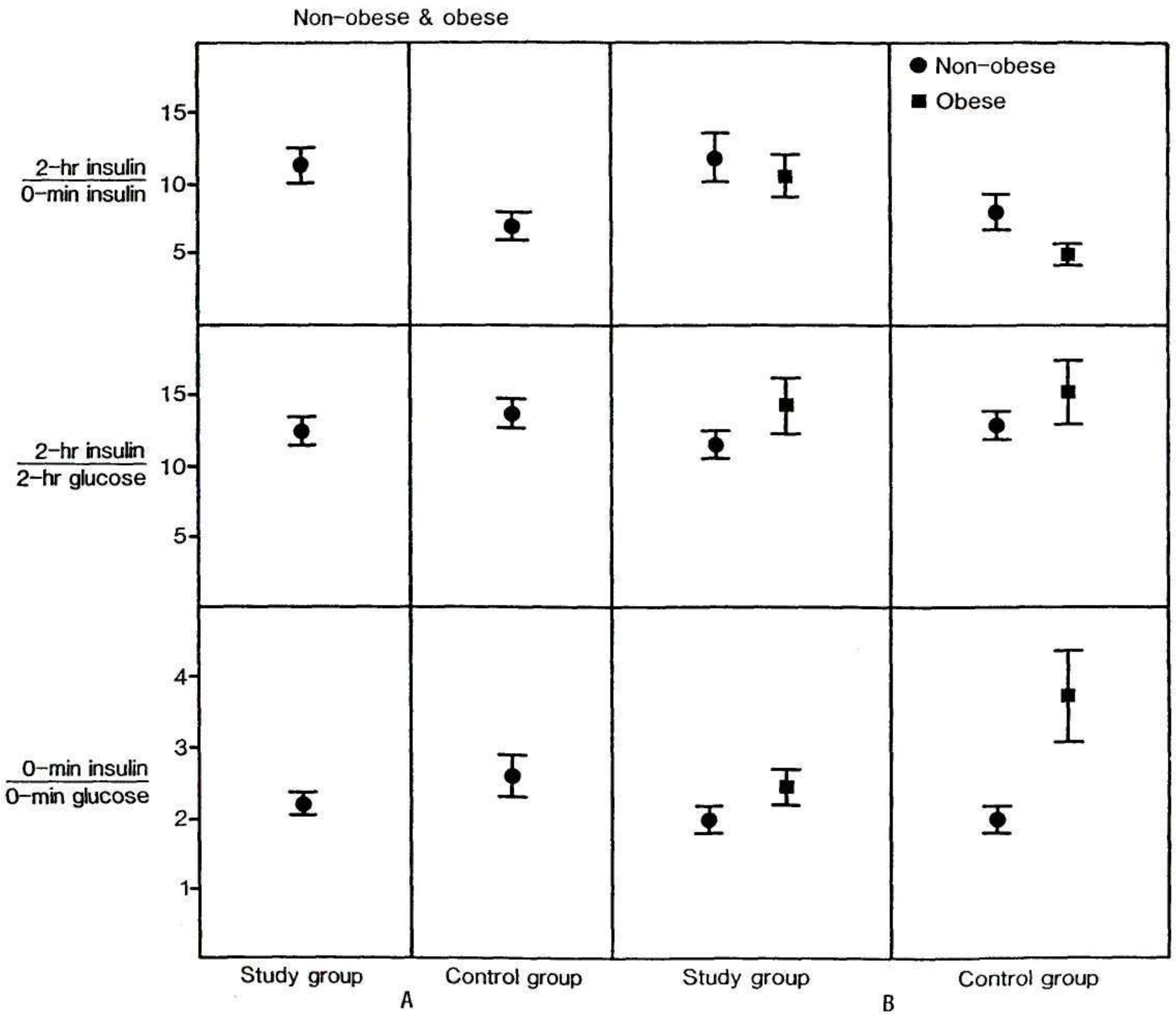


Table 12

INSULIN RATIOS AT YEAR 1 : STUDY GROUP AND CONTROL GROUP

RATIO	STUDY GROUP (n=128)	CONTROL GROUP (60)	p
Fasting insulin / Fasting glucose	2.21 ± 0.16 (0.16-11.06)	2.58 ± 0.27 (0.19-9.66)	0.03
2hr insulin / 2hr glucose	12.69 ± 0.98 (0.25-70.42)	13.74 ± 1.07 (2.32-41.47)	ns
2hr-insulin / fasting insulin	11.32 ± 1.23 (0.76-121.58)	7.10 ± 0.88 (1.27-50.4)	0.02

Table 13

MEAN INSULIN RATIOS AT YEAR 1 : STUDY GROUP AND CONTROL GROUP BASED ON BMI

RATIO	+BMI	STUDY GROUP *(n=74,54)	CONTROL GROUP *(n=40,20)	**p
0-min insulin / 0-min glucose	NON-OBESE	2.02 ± 0.17(0.16-7.0)	1.99 ± 0.18(0.2-4.93)	-
	OBESE	2.47 ± 0.28(0.32-11.06)	3.76 ± 0.64(0.88-9.66)	0.036
	≠p	-	0.015	
120min insulin / 120min glucose	NON-OBESE	11.50 ± 0.92(0.25-39.8)	12.97 ± 1.10(2.32-32.25)	-
	OBESE	14.32 ± 1.94(1.74-70.42)	15.24 ± 2.34(3.94-41.47)	-
	≠p	-	-	
120min insulin / 0min glucose	NON-OBESE	11.80 ± 1.87(0.76-121.58)	8.16 ± 1.24(1.60-50.4)	-
	OBESE	10.66 ± 1.41(1.03-48.83)	5.04 ± 0.78(1.27-14.53)	0.0008
	≠p	-	0.038	

+OBESITY: BMI ≥ 27 in males
≥ 25 in males
*n=number: non-obese, obese, respectively
**p values for study group vs control group
≠p values for non-obese vs obese
-p not significant

b) In obese subjects, the Mean fasting insulin : glucose ratio was significantly lower in the study group 2.47 ± 0.28 compared to the control group 3.76 ± 0.64, p=0.036. The mean 2-hr insulin : fasting insulin ratio was significantly higher in the study group 10.66 ± 1.41 compared to the Control group 5.04 ± 0.78 p=0.0008.

c) In the Study group, no significant difference was observed between obese and non-obese subjects, for each of the three ratios. In the Control group, the Mean fasting insulin : glucose ratio was significantly higher (p=0.015) and the Mean 2-hr insulin : fasting insulin ratio significantly lower (p=0.038) in obese subjects compared to non-obese subjects.

B. BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

1. Obese and non-obese combined:

Table 14, Figure 6

Comparison between the 4 groups revealed no significant difference in Mean fasting insulin : glucose ratio.

Significant interaction between the 4 groups was observed for Mean 2-hr insulin : glucose ratio and Mean 2-hr insulin : fasting insulin ratio (p=0.001, p=0.003, respectively). The Mean 2-hr insulin : glucose ratio was significantly lower in the $Diabetes_1$ groups compared to each of the other 3 groups (IGT_1, $Normal_1$ and Control).

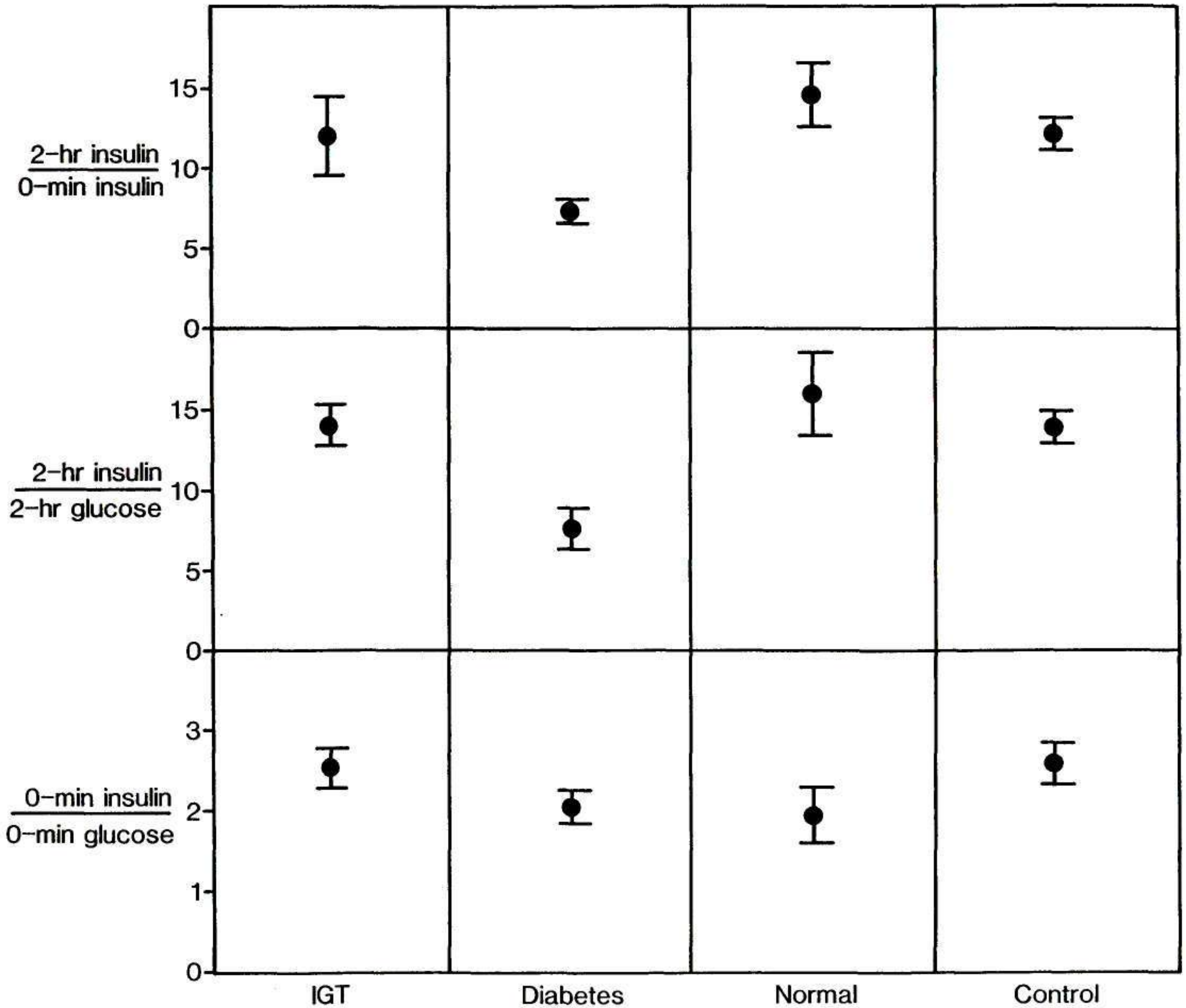


Figure 6:

Insulin Ratios at Year 1: based on category of glucose tolerance.

Table 14

MEAN INSULIN RATIOS AT YEAR 1 : STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE AND CONTROL GROUP

RATIO	CATEGORY OF GLUCOSE TOLERANCE				*p
	IGT_1 (n=47)	$DIABETES_1$ (n=41)	$NORMAL_1$ (n=40)	CONTROL (n=60)	
0-min insulin / 0-min glucose	2.57	2.05	1.94	2.58	-
2-hr insulin / 2-hr glucose	14.13^{A}	7.64^{B}	16.17^{A}	13.74^{A}	0.0001
2-hr insulin / 0-min insulin	$12.08^{A,B}$	7.24^{B}	14.61^{A}	7.10^{B}	0.003

*p values are for comparisons between the four groups by analysis of variance.
A,B: Mean values with the same letter are not significantly different.

2. Based on BMI

Table 15, 16, Figure 7

a) In non- obese subjects, a significant interaction between the 4 groups was demonstrated for 2hr-insulin : glucose ratio only (p=0.0059); the Mean ratio being highest in the IGT_1 group, with a significant difference between the IGT_1 group (14.79) and $Diabetes_1$ group (7.36).

b) In obese subjects, significant interaction between the 4 groups was observed for the Mean 2-hr insulin : glucose ratio and Mean 2-hr insulin : fasting insulin ratio (p=0.0007, p=0.0013, respectively), both of which were significantly higher in the $Normal_1$ group compared to each of the remaining three groups (IGT_1, $Diabetes_1$, Control).

c) In the IGT_1 and $Diabetes_1$ groups, there was no significant difference between obese and non-obese subjects, for any of the ratios examined. In the $Normal_1$ group, the Mean 2-hr insulin : glucose ratio was significantly higher in obese subjects (26.33) compared to non-obese subjects (11.27) p=0.02.

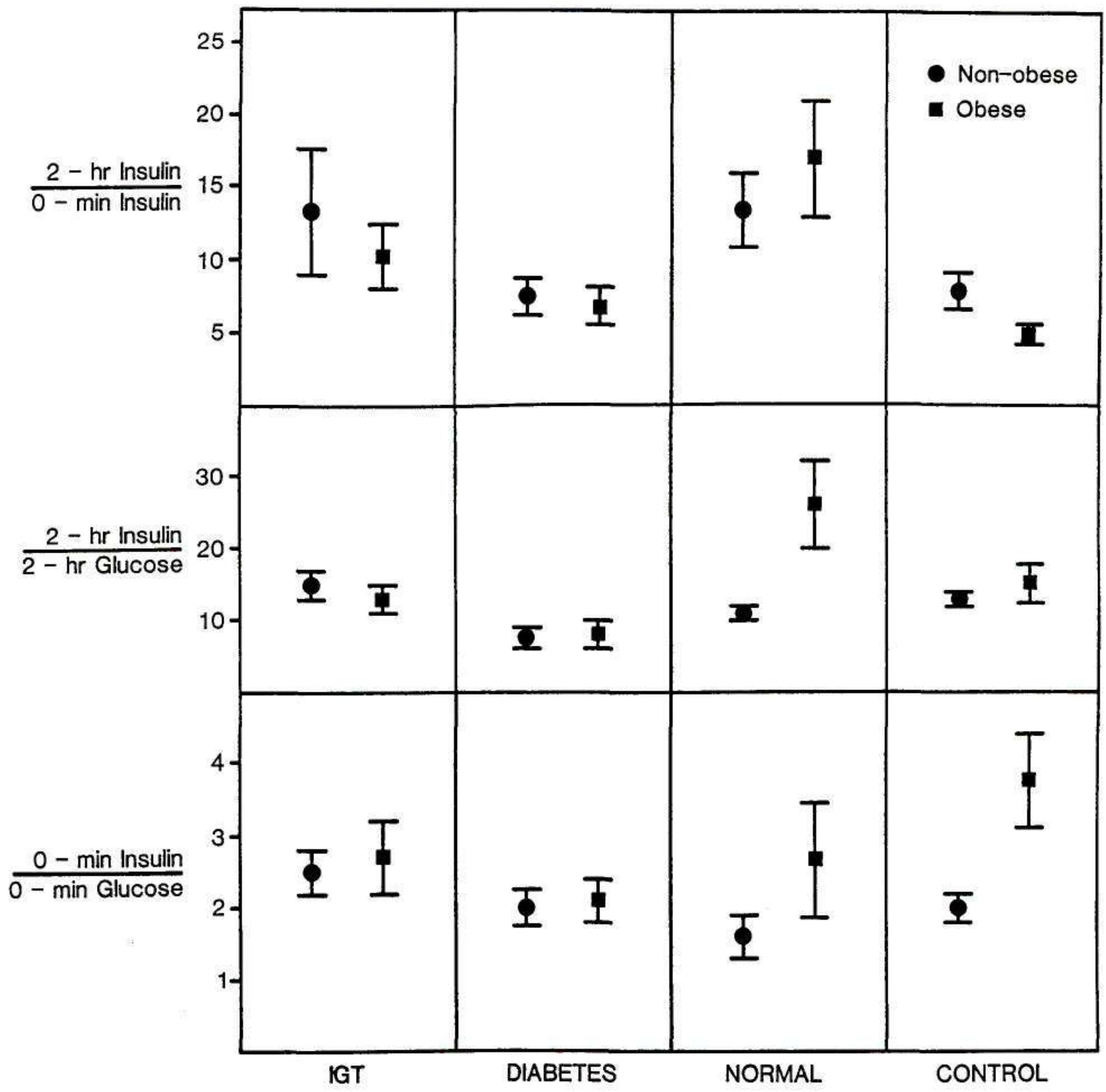


Figure 7: Insulin Ratios at Year 1: based on category of glucose tolerance and BMI.

Table 15

MEAN INSULIN RATIOS AT YEAR 1, BASED ON CATEGORY OF GLUCOSE TOLERANCE AND +BMI

RATIO	CATEGORY OF GLUCOSE TOLERANCE				*p
	IGT_1	$DIABETES_1$	$NORMAL_1$	CONTROL	
	NON-OBESE				
	n=47	n=20	n=27	n=40	
0-min insulin / 0-min glucose	2.47	1.98	1.60	1.99	ns
120-min insulin / 120-min glucose	14.79^{A}	7.36^{B}	$11.27^{A,B}$	12.97^{A}	0.0059
120-min insulin / 120-min glucose	13.38	7.49	13.42	8.16	ns
	OBESE				
	n=20	n=21	n=13	n=20	
0-min insulin / 0-min glucose	2.71	2.12	2.67	3.76	ns
120-min insulin / 120-min glucose	13.25^{B}	7.91^{B}	26.33^{A}	15.24^{B}	0.0007
120-min insulin / 0-min insulin	10.33^{B}	6.99^{B}	17.09^{A}	5.04^{B}	0.0013

*p values are for comparisons between the four groups by analysis of variance.
A,B: Means with the same letter are not significantly different.
+OBESITY: BMI ≥ 27 in males
≥ 25 in females

Table 16

MEAN INSULIN RATIOS AT YEAR 1 BASED ON CATEGORY OF GLUCOSE TOLERANCE: NON-OBESE vs OBESE

*BMI CATEGORY (n)	RATIO		
	0-min insulin / 0-min glucose	120-min insulin / 120-min glucose	120-min insulin / 0-min insulin
	IGT_1		
NON-OBESE (27)	2.47	14.79	13.38
OBESE (20)	2.71	13.25	10.33
p	-	-	-
	$DIABETES_1$		
NON-OBESE (20)	1.98	7.36	7.49
OBESE (21)	2.12	7.91	6.99
p	-	-	-
	$NORMAL_1$		
NON-OBESE (27)	1.60	11.27	13.42
OBESE (13)	2.67	26.33	17.09
p	-	0.02	
	CONTROL		
NON-OBESE (40)	1.99	12.97	8.16
OBESE (20)	3.76	15.24	5.04
p	0.015	-	0.038

*OBESITY: BMI ≥ 27 in males
≥ 25 in females
-p not significant

IV AREA UNDER THE PLASMA INSULIN CURVE (INSULIN AREA; TOTAL INTEGRATED INSULIN RESPONSE)

Results are summarised in Table 17 and 18, Figure 8,9

A. TOTAL STUDY GROUP

Table 17, Figure 8

1. Non-obese and obese comnbined:

The Mean Insulin Area was significantly lower in the study group 166.67 ± 10.6 μu/ml·hr compared to that in the Control group 186.78 ± 13.8 μu/ml·hr, p=0.015.

2. Based on BMI:

In non-obese subjects, no significant difference was observed between the study group (156.73 ± 12.51 μu/ml·hr) and Control group (165.29 ± 14.81 μu/ml·hr).

In obese subjects the Mean Insulin Area was significantly lower in the study group 180.29 ± 18.35 μu/ml·hr compared to the Control group 228.67 ± 26.8 μu/ml·hr, p=0.012.

B. BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

Table 18, Figure 9

1. Non-obese and obese combined

The Mean Insulin Area was highest in the IGT_1 group (196.87 ± 18.54 μu/ml·hr), lowest in the $Diabetes_1$ group (146.19 μu/ml·hr) with

Figure 8: Area under the plasma insulin curve at Year 1: total study group and control group.

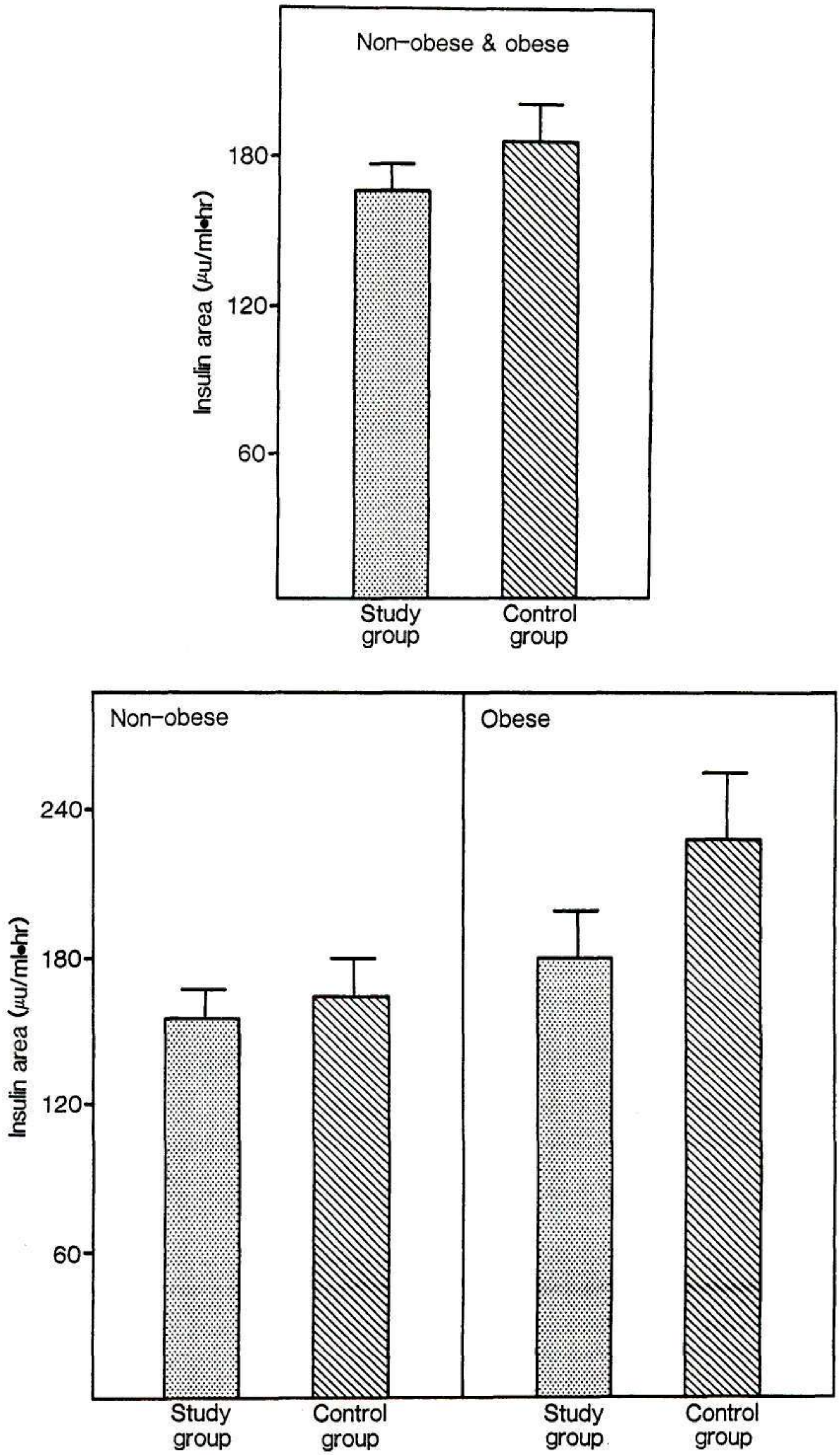


Table 17

AREA UNDER PLASMA INSULIN CURVE/INSULIN AREA (μu/ml·hr) AT YEAR 1
STUDY GROUP AND CONTROL GROUP

	INSULIN AREA (μu/ml·hr)	
	*ARITHMETIC VALUES	+Log values
≠NON-OBESE + OBESE		
Study Group (128)	166.67 ± 10.6 (7.3-627.88)	4.86
Control Group (60)	186.78 ± 13.8 (58.05-544.43)	5.09
p	ns	0.015
NON-OBESE		
Study Group (74)	156.73 ± 12.51 (7.3-512.13)	4.82
Control Group (40)	165.29 ± 14.81 (58.05-460.05)	4.98
p	ns	ns
OBESE		
Study Group (54)	180.29 ± 18.35 (15.3-627.88)	4.92
Control Group (20)	228.67 ± 26.8 (95.13-544.43)	5.32
p	ns	0.012

*Mean ± SE (Range)
+Mean value
≠OBESITY: BMI ≥ 27 in males
≥ 25 in females

intermediate values in the remaining two groups (186.78 ± 13.8 and 152.17 ± 19.42 μu/ml·hr for Control and $Normal_1$ groups, respectively).

Comparison between the 4 groups by ANOVA revealed significant interaction (p=0.0076). Although the levels were higher in the IGT_1 group, no significant difference was observed when the IGT_1 group was compared to the Control group. The Mean Insulin Area was significantly lower in the $Diabetes_1$ group and $Normal_1$ group, when these were compared to the IGT_1 group and Control group, respectively.

2. Based on BMI:

a) In non-obese subjects, the Mean Insulin Area was highest in the IGT_1 group (201.96 ± 25.89 μu/ml·hr), lowest in the $Normal_1$ group (116.59 ± 12.83 μu/ml·hr) with intermediate values in the remaining two groups (165.29 ± 14.81 and 149.85 ± 20.47 μu/ml·hr for the Control group and $Diabetes_1$ group, respectively).

Intergroup comparison by ANOVA, revealed significant interaction (p=0.019). Although the level was higher in the IGT group compared to the Control group, no significant difference was observed between the two groups.

b) In obese subjects, no significant interaction was observed between the four groups.

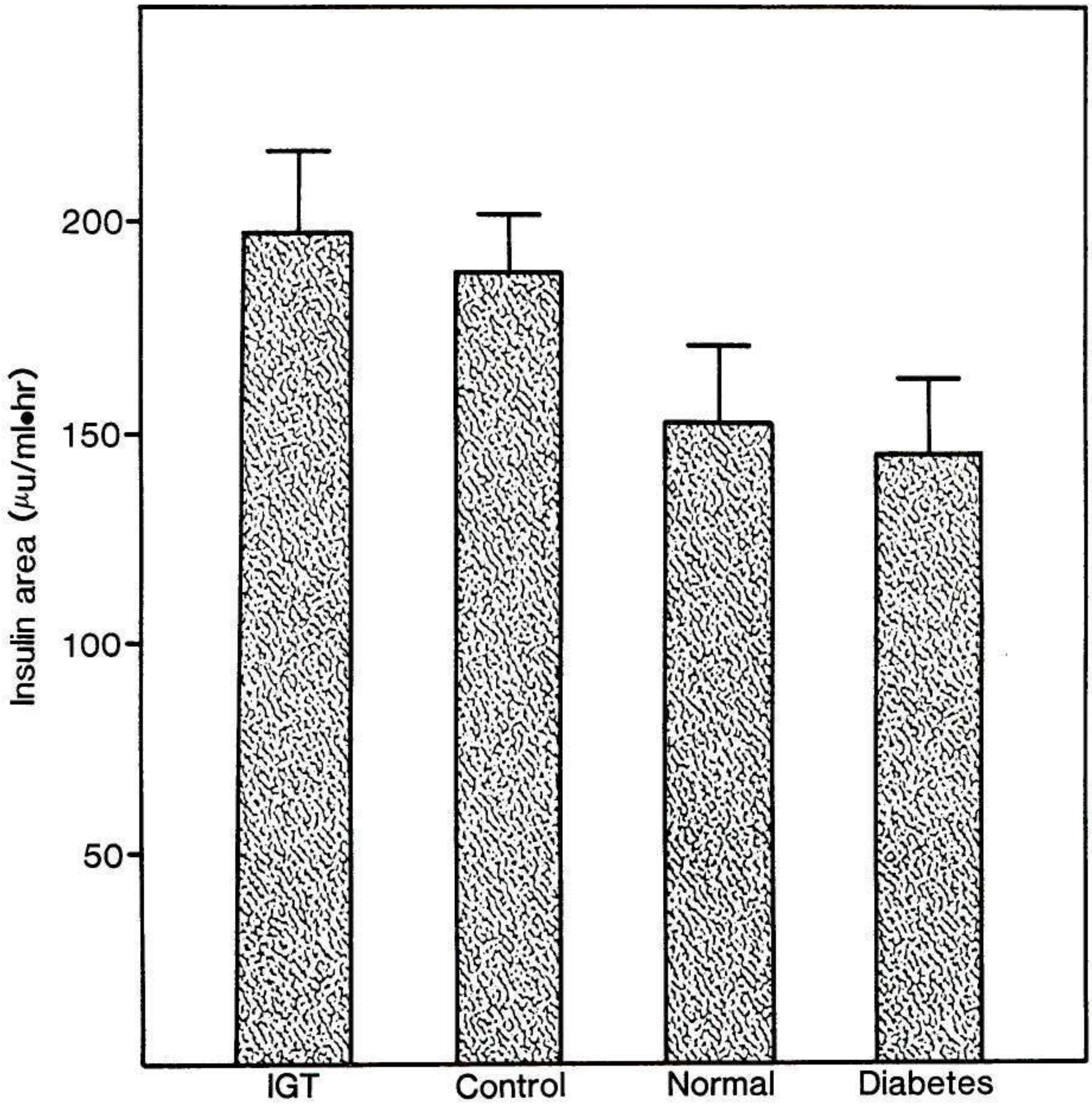


Figure 9: Area under the plasma insulin curve at Year 1: based on category of glucose tolerance.

Table 18

AREA UNDER THE PLASMA INSULIN CURVE/INSULIN AREA (μu/ml·hr) AT YEAR 1 : BASED ON CATEGORY OF GLUCOSE TOLERANCE AND BMI**

	CATEGORY OF GLUCOSE TOLERANCE				$^{+}$p
	IGT$_1$	DIABETES$_1$	NORMAL$_1$	CONTROL	
NON-OBESE + OBESE					
	n=47	n=41	n=40	n=60	
	196.87 ± 18.54(47.58-512.13)	146.19 ± 16.11(7.3-521.2)	152.17 ± 19.42(15.3-627.88)	186.78 ± 13.8(58.05-544.43)	ns
*Log	5.08^{A}	4.73^{B}	4.73^{B}	5.09^{A}	0.0076
NON-OBESE					
	n=27	n=20	n=27	n=40	
	201.96 ± 25.89(54.0-512.13)^{A}	149.85 ± 20.47(7.3-321.9)^{A,B}	116.59 ± 12.83(29.68-297.55)^{B}	165.29 ± 14.81(58.05-460.05)^{A,B}	0.019
Log	5.10^{A}	4.74^{A,B}	4.59^{B}	4.98^{A}	0.019
OBESE					
	n=20	n=21	n=13	n=20	
	189.99 ± 26.69(47.58-416.8)	142.71 ± 25.17(38.98-521.2)	226.05 ± 48.55(15.3-627.88)	228.67 ± 26.8(95.13-544.43)	ns
Log	5.05^{A,B}	4.72^{B}	5.04^{A,B}	5.32^{A}	0.08

*Mean values

$^{+}$p values are for comparisons between the four groups by analysis of variance.

A,B: Mean values with the same letter are not significantly different

**OBESITY: BMI ≥ 27 in males
≥ 25 in females

V LOGARITHMS (LOG) OF I - IV

Results summarised in Table 19 - 23, 17 & 18

LOGARITHMS OF PLASMA INSULIN RESPONSE

A. TOTAL STUDY GROUP

1. Non-obese and obese combined
2. Based on BMI

Table 19 and 20, Table 1 - 3

When the logarithm (log) of plasma insulin concentration was used in statistical analysis, apart from improving the degree of significance, the results were similar to that obtained using arithmetic means. This was true whether the group was analysed as a whole, or based on BMI (cf Table 1 - 3 and Table 19 - 20).

Where the difference did arise, was in comparison between obese and non-obese subjects in the Control group (Table 3 cf Table 20). Using log (insulin), the Mean insulin was significantly higher in obese subjects at 0, 15, 30, 60 and 90 min, compared to a significant difference being noted only at 0, 15 and 60 minutes when arithmetic means were used in statistical analysis.

B. BASED ON CATEGORY OF GLUCOSE TOLERANCE

1. Non-obese and obese combined:

Table 21 cf Table 5

Similar results were obtained using log (insulin) as with the use of arithmetic means; the exception being that at 0 min, a significant degree of interaction was demonstrated using log (insulin) ($p=0.0028$).

2. Based on BMI:

Table 22, 23 cf Table 7, 8, 10

In non-obese subjects, apart from improving the degree of significance, the results using log (insulin) were similar to those using arithmetic means in statistical analysis.

In obese subjects, results were similar whether log (insulin) or arithmetic means were employed in statistical analysis.

Table 19

+MEAN PLASMA INSULIN RESPONSE DURING OGTT AT YEAR 1 :
STUDY GROUP AND CONTROL GROUP

OGTT TIME	STUDY GROUP	CONTROL GROUP	P
	NON-OBESE + OBESE		
	(n = 128)	(n = 60)	
0 min	10.80	10.70	ns
15 min	26.58	40.45	0.0001
30 min	46.06	86.49	0.0001
60 min	71.52	102.51	0.0006
90 min	81.45	88.23	ns
120 min	83.10	59.15	0.008
	NON-OBESE		
	(n = 74)	(n = 40)	
0 min	9.68	8.67	ns
15 min	26.31	34.81	ns
30 min	45.15	76.71	0.0001
60 min	71.52	91.84	0.053
90 min	76.71	78.26	ns
120 min	75.19	56.26	0.049
	OBESE*		
	(n = 54)	(n = 20)	
0 min	12.55	16.12	ns
15 min	27.39	55.15	0.0005
30 min	47.47	109.95	0.0000
60 min	71.52	127.74	0.0003
90 min	89.12	113.30	ns
120 min	94.63	64.72	ns

* OBESITY: BMI ≥ 27 in males
≥ 25 in females

+ Means and p values were computed after logarithmic transformation. geometric means are shown (antilog of the mean values).

Table 20

#MEAN PLASMA INSULIN RESPONSES DURING OGTT AT YEAR 1 :
STUDY GROUP AND CONTROL GROUP BASED ON BMI

OGTT TIME	*GROUP	NON-OBESE	+OBESE	#p
0 min	Study	9.68	12.55	ns
	Control	8.67	16.12	0.003
15 min	Study	26.31	27.39	ns
	Control	34.81	55.15	0.02
30 min	Study	45.15	47.47	ns
	Control	76.71	109.95	0.03
60 min	Study	71.52	71.52	ns
	Control	91.84	127.74	0.03
90 min	Study	76.71	89.12	ns
	Control	78.26	113.30	0.03
120 min	Study	75.19	94.60	ns
	Control	56.26	64.72	ns

* Study group: n = 74, 54; non-obese, obese respectively
Control group: n = 40, 20; non-obese, obese respectively

\+ OBESITY: BMI ≥ 27 in males
≥ 25 in females

\# Means and p values were computed after logarithmic transformation. geometric means are shown (antilog of the mean values).

Table 21

$^{+}$MEAN PLASMA INSULIN RESPONSE AT YEAR 1 BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

TIME DURING OGTT (min)	CATEGORY OF GLUCOSE TOLERANCE				*p
	IGT_1 (n = 47)	$DIABETES_1$ (n = 41)	$NORMAL_1$ (n = 40)	CONTROL (n = 60)	
	MEAN PLASMA INSULIN				
0	12.94^{A}	13.33^{A}	7.03^{B}	10.70^{A}	0.0028
15	$32.14^{A,B}$	$24.78^{B,C}$	22.87^{C}	40.45^{A}	0.0005
30	57.40^{B}	40.85^{C}	40.04^{C}	86.49^{A}	0.0001
60	90.92^{A}	60.34^{B}	64.72^{B}	102.51^{A}	0.0003
90	102.51	70.81	71.52	88.23	ns
120	106.70^{A}	75.94^{B}	68.03^{B}	59.15^{B}	0.003

*p values are for comparisons between the four groups by analysis of variance
A,B,C : Mean values with the same letter are not significantly different.
$^{+}$ Means and p values were computed after logarithmic transformation.
geometric means are shown (antilog of the mean value).

Table 22

#MEAN PLASMA INSULIN AT YEAR 1 : BASED ON CATEGORY OF GLUCOSE TOLERANCE AND *BMI

TIME DURING OGTT (min)	CATEGORY OF GLUCOSE TOLERANCE IGT$_1$ (n = 47)	DIABETES$_1$ (n = 41)	NORMAL$_1$ (n = 40)	CONTROL (n = 60)	+p
	MEAN PLASMA INSULIN				
	NON-OBESE				
	(n = 27)	(n = 20)	(n = 27)	(n = 40)	
0	12.94^{A}	12.30^{A}	6.17^{B}	$8.67^{A,B}$	0.0009
15	34.47^{A}	$23.81^{A,B}$	21.33^{B}	34.81^{A}	0.034
30	$58.56^{A,B}$	$41.26^{B,C}$	36.97^{C}	76.71^{A}	0.0004
60	93.69^{A}	59.74^{B}	61.56^{B}	91.84^{A}	0.0274
90	103.54^{A}	$72.24^{A,B}$	58.56^{B}	$78.26^{A,B}$	0.0453
120	108.85^{A}	73.70^{B}	53.52^{B}	56.26^{B}	0.0009
	OBESE				
	(n = 20)	(n = 21)	(n = 13)	(n = 20)	
0	13.07	14.30	9.03	16.12	ns
15	29.37^{B}	25.79^{B}	26.58^{B}	55.15^{A}	0.006
30	55.70^{B}	40.45^{B}	47.47^{B}	109.95^{A}	0.0003
60	$86.49^{A,B}$	60.34^{B}	70.11^{B}	127.74^{A}	0.012
90	102.50	69.41	106.70	113.30	ns
120	104.58	78.26	109.95	64.72	ns

+p values are for comparisons between the four groups by analysis of variance

A,B,C : Mean values with the same letter are not significantly different.

*OBESITY: BMI ≥ 27 in males
≥ 25 in females

Means and p values were computed after logarithmic transformation. geometric means are shown (antilog of the mean values).

Table 23

*MEAN PLASMA INSULIN RESPONSE DURING OGTT AT YEAR 1 BASED ON CATEGORY OF GLUCOSE TOLERANCE : NON-OBESE vs OBESE

+CATEGORY BASED ON BMI (n)	TIME DURING OGTT (MINUTES)					
	0	15	30	60	90	120
	MEAN PLASMA INSULIN					
	IGT$_1$					
NON-OBESE (27)	12.9	34.47	58.56	93.69	103.54	108.85
OBESE (20)	13.06	29.37	55.70	86.46	102.51	104.58
p	ns	ns	ns	ns	ns	ns
	DIABETES$_1$					
NON-OBESE (20)	12.30	23.81	41.26	59.74	72.24	73.70
OBESE (21)	14.30	25.79	40.45	60.34	69.41	78.26
p	ns	ns	ns	ns	ns	ns
	NORMAL$_1$					
NON-OBESE (27)	6.17	21.33	36.97	61.56	58.56	53.52
OBESE (13)	9.30	26.58	47.47	70.11	106.70	109.95
p	ns	ns	ns	ns	ns	0.046
	CONTROL					
NON-OBESE (40)	8.67	34.81	76.71	91.84	78.26	56.26
OBESE (20)	16.12	55.12	109.95	127.74	113.30	64.72
p	0.003	0.02	0.03	0.03	0.03	ns

+ OBESITY: BMI ≥ 27 in males
≥ 25 in males

p values are for comparison between non-obese and obese.

* Means and p values were computed after logarithmic transformation. geometric means are shown (antilog of mean values).

VI CORRELATION ANALYSES

Results summarised in Table 24 - 27

Table 25 demonstrates that in the Control group, there is a significant correlation between plasma glucose and plasma insulin for each of the time points during OGTT; however, no significant correlation has been demonstrated for any of the study groups (IGT_1, $Normal_1$, $Diabetes_1$) except at 0 min in the $Diabetes_1$ group.

Table 24

PEARSON'S SIMPLE CORRELATION CO-EFFICIENT (r) BETWEEN PLASMA INSULIN AND PLASMA GLUCOSE, INSULINOGENIC INDEX AND INSULIN AREA DURING OGTT : STUDY GROUP + CONTROL GROUP (188 SUBJECTS)

PLASMA INSULIN DURING OGTT	GLUCOSE	INSULINOGENIC INDEX	INSULIN AREA
0 min	0.26 (p0.0003)		0.44 (p0.0001)
15 min	0.06 (p -)	0.36 (p0.0001)	0.67 (p0.0001)
30 min	0.01 (p -)	0.41 (p0.0001)	0.76 (p0.0001)
60 min	-0.004 (p -)	0.12 (p -)	0.86 (p0.0001)
90 min	0.06 (p -)	0.19 (p0.01)	0.89 (p0.0001)
120 min	0.13 (p -)	0.24 (p0.0011)	0.84 (p0.0001)

Results expressed as r (p value)
p - not significant

Table 25

PEARSON'S CORRELATION CO-EFFICIENT (r) BETWEEN PLASMA INSULIN AND PLASMA GLUCOSE, INSULINOGENIC INDEX AND INSULIN AREA : BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

INSULIN	CORRELATION Co-efficient (r)		
OGTT TIME	GLUCOSE	INSULINOGENIC INDEX	INSULIN AREA
	IGT_1		
0 min	0.13		0.45**
15 min	0.02	0.58***	0.78***
30 min	0.07	0.22	0.89***
60 min	-0.05	0.88***	0.92***
90 min	0.16	0.27	0.95***
120 min	0.10	0.27	0.89***
	$DIABETES_1$		
0 min	0.36*		0.37*
15 min	0.22	0.54***	0.65***
30 min	0.23	0.75***	0.64***
60 min	-0.04	0.97***	0.91***
90 min	-0.26	0.96***	0.93***
120 min	-0.23	0.89***	0.94***
	$NORMAL_1$		
0 min	0.11		0.43**
15 min	0.22	0.45**	0.50***
30 min	-0.002	0.45**	0.63***
60 min	0.11	0.15	0.79***
90 min	0.29	0.36*	0.90***
120 min	0.21	0.51***	0.92***
	CONTROL		
0 min	0.27*		0.52***
15 min	0.41**	0.31*	0.78***
30 min	0.35**	0.42***	0.88***
60 min	0.62***	-0.03	0.84***
90 min	0.56***	0.03	0.96***
120 min	0.51***	0.20	0.82***

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 26

PEARSON'S SIMPLE CORRELATION CO-EFFICIENT (r) BETWEEN INSULIN AREA AMD PLASMA INSULIN, GLUCOSE, INSULINOGENIC INDEX (II) DURING OGTT: BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

INSULIN AREA	CORRELATION COEFFICIENT -r		
OGTT TIME	INSULIN	GLUCOSE	II
	IGT_1		
0 min	0.45**	-0.03	
15 min	0.78***	-0.08	0.59***
30 min	0.89***	-0.02	0.22
60 min	0.92***	-0.01	0.74***
90 min	0.95***	0.08	0.32*
120 min	0.89***	0.08	0.15
	$DIABETES_1$		
0 min	0.37*	0.03	
15 min	0.65***	-0.09	0.61***
30 min	0.64***	-0.06	0.66***
60 min	0.91***	-0.15	0.90***
90 min	0.93***	-0.19	0.85***
120 min	0.94***	-0.22	0.82***
	$NORMAL_1$		
0 min	0.43**	0.04	
15 min	0.50***	0.01	0.29⁻
30 min	0.63***	0.05	0.26
60 min	0.79***	0.19	0.04
90 min	0.90***	0.27	0.41**
120 min	0.92***	0.19	0.54***
	CONTROL		
0 min	0.52***	0.08	
15 min	0.78***	0.30*	0.18
30 min	0.88***	0.50***	0.20
60 min	0.84***	0.45***	-0.08
90 min	0.96***	0.53***	-0.05
120 min	0.82***	0.38***	0.13

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
$-p = 0.06$

Table 27

PEARSON'S SIMPLE CORRELATION CO-EFFICIENT (r) BETWEEN INSULINOGENIC INDEX (II) AND PLASMA INSULIN, GLUCOSE, INSULIN AREA DURING OGTT : BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

II	CORRELATION COEFFICIENT (r)		
OGTT TIME	INSULIN	GLUCOSE	INSULIN AREA
	IGT_1		
15 min	0.58***	-0.26	0.59***
30 min	0.2	-0.46**	0.22
60 min	0.88***	-0.33*	0.74***
90 min	0.27	-0.36*	0.32*
120 min	0.27	-0.22	0.15
	$DIABETES_1$		
15 min	0.54***	0.03	0.61***
30 min	0.75***	-0.07	0.66***
60 min	0.97***	-0.17	0.90***
90 min	0.96***	-0.41**	0.85***
120 min	0.89***	-0.39*	0.82***
	$NORMAL_1$		
15 min	0.45**	-0.1	0.29⁻
30 min	0.45**	-0.3	0.26
60 min	0.15	-0.46**	0.04
90 min	0.36*	-0.26	0.41**
120 min	0.51***	-0.08	0.54***
	CONTROL		
15 min	0.29	-0.02	0.18
30 min	0.42	-0.29*	0.20
60 min	-0.04	-0.39**	-0.08
90 min	0.02	-0.19	0.05
120 min	0.27*	0.21	0.13

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
−p = 0.06

DISCUSSION

IGT is associated with an increased risk for the development of NIDDM. Therefore a study of various metabolic characteristics of IGT such as the plasma insulin response to a secretagogue could help elucidate the pathogenesis of NIDDM.

The aim of such a study would be 1) to establish the pattern of insulin response to a glucose load in IGT subjects (i.e hypoinsulinaemia/hyperinsulinaemia/heterogeneity); 2) to determine whether insulin resistance (impaired insulin action) is a characteristic; and 3) to determine whether any of these factors serves as a marker for subsequent deterioration to NIDDM in subjects with IGT.

Ever since the development of a sensitive and specific radioimmunoassay for the measurement of insulin (Yalow and Berson 1960), there have been numerous studies describing the insulin response to glucose in subjects with different categories of glucose tolerance. Controversy existed as to whether hypo-hyperinsulinaemia following an oral carbohydrate load is the characteristic of subjects with mild to moderate carbohydrate intolerance. Earlier studies had reported decreased insulin response to oral glucose in subjects with borderline CHO intolerance (Cerasi et al 1973, Colwell JA and Lein A 1967), but those reports were challanged by other workers who reported hyperinsulinaemia in such subjects (Reaven et al 1971, Rosenbloom A 1970, Jackson et al 1972, Chiles et al 1970, Danowski et al 1973, Reaven G and Miller R 1968, Seltzer et al 1967). Much of the earlier controversies could possibly be explained by the wide range of criteria employed for glucose tolerance.

In a study on a wide spectrum of glucose tolerance in Pima Indians (Savage et al 1975), it was found that 2-hr insulin levels were highest in the borderline group and lowest in the NIDDM group, while fasting insulin levels were similar in all groups of glucose tolerance; the conclusion was that their data could not support the concept of hypo-or hyperinsulinaemia as the initial lesion in diabetes. What emerged from that study, however, was that subjects with borderline glucose tolerance (2-hr glucose 6.7 - 9.4 mmol/L and 9.4 - 13.3 mmol/L) were hyperinsulinaemic although there was considerable variation among individual responses in this group.

The finding of hyperinsulinaemia in response to a CHO load in subjects with borderline CHO intolerance was confirmed in subsequent studies (Reaven et al 1976, Reaven and Olefsky 1977).

Several epidemiological studies, apart from that of Savage et al (1975), have examined the plasma insulin response to an oral glucose load, either as part of crosssectional studies (Savage et al 1975, Zimmet et al 1978, Martin et al 1980, Lillioja et al 1988) or of longitudinal studies (Sartor et al 1980, Keen et al 1982, Kadowaki et al 1984, Knowler et al 1986, Sicree et al 1987, Lillioja et al 1988, Saad et al 1988).

In a study of 189 Nauruans with a wide range of glucose tolerance (Zimmet et al 1978), it was found that the 2-hr plasma insulin levels were highest in the group with 2-hr plasma glucose levels of 140-199mg/100ml (corresponding to present criteria for IGT), with a progressive fall in 2-hr insulin response with increasing glucose intolerance; in the group with a 2-hr plasma glucose ≥ 400mg/100ml (≥ 22mmol/L) the 2-hr plasma insulin was significantly lower than that in all the other groups studied. Of note was the finding that fasting plasma insulin levels were similar in all categories of glucose tolerance and that obesity was found to be the most important factor influencing both fasting and 2-hr insulin levels.

In a study in Papua New Guinea (Martin et al 1980), no difference was found in fasting plasma insulin levels in urban Melanesians with a wide range of glucose tolerance. In contrast 2-hr insulin levels were highest in the group with 2-hr blood glucose levels of 9.1 - 11.1 mmol/L, thereafter showing a decline at higher blood glucose levels.

In the cross-sectional study on IGT in Pima Indians with varying degrees of glucose tolerance, the fasting plasma insulin during OGTT was significantly higher in IGT subjects compared to Normal subjects, but significantly lower when compared to Diabetic subjects with fasting blood glucose ≥ 7 mmol/L (Lillioja et al 1988).

Much of the understanding of the role of insulin in glucose intolerance has emerged from the numerous and elegant studies by Reaven and co-workers, whose contributions have spanned more than two decades. In a study of 125 patients who were divided into four categories of glucose tolerance, it was demonstrated that while fasting insulin levels were similar in all groups, the 2-hr insulin response during OGTT was highest in the impaired tolerance group. Of note, though, was that the criteria for glucose tolerance in that study differed from presently acceptable criteria. However, what also emerged from that study was the great variability in the magnitude of individual insulin responses, exemplified by the relatively large standard errors (Reaven G and Miller R 1968).

These findings were confirmed in another study of 95 subjects, in which during OGTT subjects with "chemical diabetes" had fasting plasma insulin levels similar to (although higher), and 2-hr levels significantly higher than, subjects with normal glucose tolerance. Moreover, subjects with severe fasting hyperglycaemia (glucose > 8.3 mmol/L) had significantly lower insulin levels compared to Normal subjects at all points during OGTT (Reaven et al 1976).

A third study confirmed the findings of the two quoted above; moreover it served to highlight the concept of variability and heterogeneity of insulin response in subjects with chemical diabetes (Reaven GM and Olefsky JM 1977).

To date, only a few studies on insulin response in South African Indian subjects withIGT (using WHO criteria) have been reported. In an earlier study on Tamil Indians, it was demonstrated that subjects with "Borderline GTT" had higher fasting insulin and insulin response during OGTT; it was concluded that the earliest biochemical lesion in diabetes is insulin excess rather than deficiency (Jackson et al 1972). It must be noted though, that different criteria for glucose tolerance were employed in Jackson's study. In the baseline study from which subjects for the present study were selected (Omar et al 1986), fasting and 2-hr insulin levels were examined in a subset of patients - in that study, although both fasting and 2-hr insulin levels were higher in IGT subjects compared to Control subjects, there was no significant difference observed. In a study of 26 hospital based subjects with IGT (Jialal et al 1986), no significant difference was found in mean insulin responses when compared to control subjects, except that obese IGT subjects had significantly higher 2-hr insulin levels compared to obese control subjects.

The finding in the present study, that the study group demonstrated a mean fasting plasma insulin level which was higher but not significantly different from that of the Control group, is compatible with most of the studies quoted (Savage et al 1975, Zimmet et al 1978, Martin et al 1980, Reaven G and Miller R 1968, Reaven et al 1976, Reaven GM and Olefsky JM 1977, Reaven et al 1989) and at variance with the two studies on Pima Indians in which IGT subjects were found to have significantly higher fasting insluin levels compared to subjects with Normal Glucose tolerance (Lillioja et al 1988, Saad et al 1988). The observation in the present study, viz, that the study group exhibited significantly higher 2-hr plasma insulin response (hyperinsulinaemia) compared to the Control group, confirms the findings of the aforementioned studies except those of Lillioja (1988) and Saad (1988) - (however, the study by Saad et al (1988) was a longitudinal study and reported on baseline characteristics according to outcome in IGT subjects; the study by Lillioja et al (1988) did not examine 2-hr insulin level during OGTT). Therefore, the results of the present study lends support to the concept of hyperinsulinaemia in subjects with IGT.

The above comparisons between the present and quoted studies takes into account the Total study group; of note, is that whilst all the study subjects were IGT a year previously, at the time that the insulin response during OGTT was examined, these subjects had already entered into the first year of the natural history of their IGT (Year 1) - and hence, were either IGT_1 $Normal_1$ or $Diabetes_1$ (newly diagnosed diabetes).

However, even when the Study group was divided according to the category of glucose tolerance at Year 1, the findings were much the same as when the study group was examined as a whole i.e. that hyperinsulinaemia is a feature of subjects with IGT: the mean fasting plasma insulin was higher (although not significantly so) in the IGT_1 group compared to the Control group, whilst mean 2-hr plasma insulin was significantly higher in IGT_1 group compared to the Control group. Therefore the finding in the present study of post load hyperinsulinaemia in IGT_1 subjects supports that of previously quoted studies (as with the study group as a whole). Of note in the present study is that similar results were obtained when the $Diabetes_1$ group was compared to the Control group (i.e. higher fasting and 2-hr plasma insulin) - a finding probably explicable by the fact that this group represented newly diagnosed diabetic subjects; in fact fasting plasma insulin was highest in the $Diabetes_1$ group, therefore lending support to the concept of hyperinsulinaemia (insulin excess)/insulin resistance as the initial lesion in diabetes.

Many factors are known to affect insulin levels attained during an OGTT, including age, sex, glucose level and degree of obesity, the latter two being generally considered of major importance (Savage et al 1975). In the present study, no significant difference was demonstrated in Mean plasma insulin response between obese and non-obese subjects in each of the 3 study groups (IGT_1 $Normal_1$ $Diabetes_1$); whilst in the Control group Mean levels were significantly higher in obese subjects (Table 10 and 20). Moreover, when subjects were examined on the basis of BMI (obese, non-obese), the difference between the IGT_1 group and Control group was more marked in non-obese subjects than in obese subjects (Table 7 and 8). Therefore the differences in insulin levels were probably related to variation in glucose tolerance, rather than obesity.

Heterogeneity of insulin responses in subjects with "Latent" Diabetes was described by Fajans and co-workers (1974). These observations were subsequently confirmed by many other workers (Reaven G and Miller R 1968, Savage et al 1975, Reaven et al 1976, Reaven GM and Olefsky JM 1977, Kosaka K and Akanuma Y 1980, Keen H 1980, Ratzman et al 1983, Fajans SS 1980). Certainly, in the present study, heterogeneity and variability in insulin response was a feature for all categories of glucose tolerance (IGT_1 $Diabetes_1$ $Normal_1$ and Control) as judged by the magnitude of the standard errors and wide range around the mean insulin response (Table 1 and 4).

In the present study, plasma insulin responses were examined at several points during OGTT (0, 15, 30, 60, 90 and 120 min). Several non-epidemiological studies (Reaven and co-workers 1968, 1976, 1977, 1989) have also examined insulin responses in a similar fashion. However, most of the epidemiological studies quoted above have reported only on fasting and 2-hr post load insulin response in subjects with IGT, with the exception of those undertaken in Pima Indians (Savage et al 1975 and 1975). The examination of insulin response at various time points during OGTT provides valuable information on the pattern of insulin response in various categories of glucose tolerance.

In the present study, when the study group was divided according to the category of glucose tolerance and compared to the control group, different patterns of insulin response during OGTT were demonstrated: in the control group, in response to the oral glucose load, there was a prompt and brisk increase in plasma insulin level to a peak at 60 minutes, followed by decreasing levels; in contrast, in the IGT_1 group although fasting plasma insulin levels were higher, the response to the glucose load was delayed, and insulin levels progressively increased with the duration of the OGTT, maximum levels being achieved only at 120 minutes, despite falling blood glucose levels (albeit small). The findings in the present study are compatible with those found in Pima Indians (Savage et al 1975); moreover, in that study the group with 2-hr blood glucose > 22.2 mmol/L failed to show a significant insulin response above fasting levels. The fact that in the present study, the $Diabetes_1$ group demonstrated a pattern of insulin response similar to that of the IGT_1 group, can be explained by these subjects being newly diagnosed diabetics whose mean 2-hr plasma glucose was 14.69 mmol/L; perhaps with longer duration of diabetes these subjects will show insulin responses that would be not unlike Savage's group (similar results were reported by Reaven and co-workers 1968, 1976, 1989).

With respect to the question of insulin resistance, there is no doubt that this is best assessed quantitavely by way of testing the ability of exogenously infused insulin to limit hyperglycaemia during continuous infusion of glucose and insulin - the euglycaemic clamp technique (De Fronzo et al 1979, Shen et al 1970, Reaven et al 1976, Reaven GM and Olefsky JM 1977). However, a measure of insulin resistance may also be reflected by the insulin response during OGTT (Reaven et al 1976, Reaven GM and Olefsky JM 1977, Reaven G and Miller R 1979, Hollenbeck et al 1984, Reaven et al 1989, Reaven GM 1979). Variables from plasma insulin responses during OGTT which have been found to correlate with insulin resistance using the clamp technique, include a) plasma insulin response at varying time points during OGTT b) area under the plasma insulin curve (Total integrated plasma insulin response/Insulin area) and c) Incremental Insulin (Hollenbeck et al 1984, Reaven et al 1989, Reaven et al 1986, Reaven et al 1976, Reaven G and Miller R 1979).

In a study of 95 non-obese subjects with varying degrees of glucose tolerance, patients with chemical diabetes were found to have an insulin response during OGTT which was equal to or greater than that of normal subjects, yet they were unable to dispose of the glucose load as efficiently (as assessed by the clamp technique) - the conclusion was that the abnormal CHO metabolism in this group was a direct function of insulin resistance rather than insulin deficiency (Reaven et al 1976).

The relationship between plasma glucose response, plasma insulin response and SSPG response (clamp technique) was undertaken in 145 non-obese subjects with Normal glucose tolerance/chemical diabetes/overt diabetes: in that study, a positive correlation was found between insulin resistance (as assessed by SSPG response) and hyperinsulinaemia (as assessed by Area under the plasma insulin curve) in Normal subjects and subjects with chemical diabetes (Reaven GM and Miller RG 1979).

In a study of normal subjects, insulin resistance (as assessed by euglycaemic clamp) was found to be positively correlated with (i) plasma insulin response at various time intervals during OGTT; (ii) incremental insulin and (iii) Insulin area, the best correlation being with (iii) (Hollenbeck et al 1984).

More recently (Reaven et al 1989), the relationship between glucose tolerance, insulin secretion and insulin action (by clamp technique) was studied in 50 non-obese subjects with varying categories of glucose tolerance: in that study, it was found that plasma insulin response during OGTT was significantly higher in IGT and Diabetes group (FBG < 8 mmol/L) compared to Normal group, yet glucose uptake (insulin action) was significantly lower - according to the authors, the fact that a defect in insulin action was demonstrated in subjects who were hyperinsulinaemic, not hypoinsulinaemic, and only moderately hyperglycaemic, is consistent with the hypothesis that resistance to insulin-stimulated glucose uptake is a basic characteristic of subjects with IGT or Type 2 diabetes.

In the present study, since only OGTT were performed, variables to assess whether insulin resistance existed in IGT subjects, included plasma insulin levels at various time points during OGTT and Insulin Area.

That insulin resistance was a feature in the present study, is supported by the finding that the Mean plasma insulin was higher (hyperinsulinaemia) in the IGT_1 group compared to the Control group at 0, 60, 90 and 120 minutes (and significantly so at 120 minutes).

However using Insulin Area as a correlate of insulin resistance was less convincing; although Insulin Area was higher in IGT_1 group compared to Control group, there was no significant difference demonstrated; this finding is at variance with those studies which have demonstrated a significantly higher Mean Insulin Area in subjects with IGT, either in non-epidemiological studies (Reaven et al quoted above) or in epidemiological studies (Lillioja et al 1988).

The Insulinogenic Index (the ratio relating the increment in circulating insulin to the magnitude of glycaemic stimulus) may be used to compare B-cell secretory capacity in normal subjects and subjects with glucose intolerance (Seltzer et al 1967). In that study on subjects with mild diabetes, moderate diabetes and normal glucose tolerance, it was demonstrated that despite higher absolute hormonal output (plasma insulin) during OGTT in mild diabetic subjects, the Insulinogenic Index was lower than in Normal subjects, implying impaired secretory capacity. However, the use of the Insulinogenic Index as a means to quantitate the insulin response to a glucose load was challenged by Reaven and Miller (1968) whose contention was that the use of the Index resulted in a "circular argument": "that diabetic patients are hyperglycaemic by definition and since the degree to which they are hyperglycaemic appears in the denominator of the equation, therefore, a priori makes very likely the thesis that patient with diabetes (hyperglycaemia) will have lower Insulinogenic Index; also that implicit in those particular transformmations of the basic data are many assumptions concerning the physiological relationship between the two variables (glucose and insulin) for which no evidence had been presented"; whereas with the use of insulin response during OGTT, incremental insulin and Insulin Area, there appears to be sufficient scientific evidence that there exists a positive correlation between those measures and quantitative measures for insulin resistance i.e. by euglycaemic clamp (Reaven and Miller 1968, Reaven et al 1976, Reaven and Olefsky 1977, Reaven and Miller 1979, Hollenbeck et al 1984, Reaven et al 1989).

In the present study, the Mean Insulinogenic Index was highest in the Control group with progressively decreasing levels in the 3 study groups (Control $\rightarrow$ $Normal_1$ $\rightarrow$ IGT_1 $\rightarrow$ $Diabetes_1$) i.e the worse the glucose tolerance the lower the Insulinogenic Index, and for all time points during OGTT except 15 minutes, the Index was significantly higher in the Control group compared to the IGT_1 and $Diabetes_1$ groups, respectively. These findings would therefore support both Seltzer's thesis that B-cell secretory capacity was lower in subjects with glucose tolerance, as well as the argument by Reaven that by virtue of the nature of the ratio, the Insulinogenic Index would have to be lower in such subjects. Of note though, was the finding in the present study that the $Normal_1$ group despite having similar glucose response to the Control group, had Insulinogenic Indices lower than those in the Control group. Therefore, although this group exhibited normal glucose tolerance, there appears to be some defect in insulin secretion.

Moreover, if the Insulinogenic Index is accepted as a measure of insulin secretion, then from the findings in the present study, it would appear that the IGT_1 subjects have $\downarrow$ed B-cell secretory capacity (Because Insulinogenic Index $\downarrow$ed); yet the hyperinsulinaemia demonstrated in these subjects would suggest that pancreatic B-cell function was intact (and therefore support insulin resistance/impaired insulin action rather than impaired insulin secretion) i.e. that IGT_1 subjects have both pancreatic secretory deficiency and insulin resistance i.e. B-cell function is not sufficiently intact; in other words for the degree of hyperglycaemia, sufficient insulin is not being secreted.

However, in the light of the foregoing information with respect to correlative studies for insulin resistance, it would have to be conceded that the Insulinogenic Index would of necessity (by virtue of the method of its calculation) be lower in subjects with glucose intolerance, and therefore not as reliable a measure of B-cell secretory capacity, as are the measures for insulin resistance (viz plasma insulin levels, Insulin Area, incremental insulin).

If however, the Insulinogenic Index were a measure of insulin resistance, then the argument for its use would be more tenable i.e. if Insulinogenic Index bore a correlation to insulin action then subjects with normal glucose tolerance would be insulin sensitive (and have high Insulinogenic Index) whilst subjects with impaired glucose-tolerance would be insulin resistant/impaired insulin action/insulin insensitive (and have low Insulinogenic Index); however, there is no scientific basis for this theory.

This study on the insulin response during OGTT at Year 1, has thus demonstrated that when compared to the Control group, the IGT_1 group:

i) exhibited higher plasma insulin levels (hyperinsulinaemia), both fasting and 2-hr post load levels, athough only significantly so at 120 minutes (2 hrs)

ii) displayed a pattern of insulin response during OGTT which was different i.e. a more delayed response with maximal levels at 120 minutes.

iii) had lower Insulinogenic Index

Therefore the present study has demonstrated that South African Indian subjects are characterised by both hyperinsulinaemia (and therefore insulin resistance) and possibly insufficient pancreatic B-cell secretory capacity.

Of interest, would be to determine whether the insulin response in these subjects with IGT serves as a marker for subsequent deterioration to NIDDM.

SUMMARY

At Year 1, the plasma insulin response during a 75G OGTT was studied in 128 study subjects (67 males and 61 females) who were diagnosed as IGT a year previously (Year 0), and in 60 control subjects (28 males and 32 females). Study subjects were also divided according to the category of glucose tolerance at Year 1 (viz IGT_1 $Diabetes_1$ $Normal_1$). Both study and control subjects were further classified as obese or non-obese, based on BMI.

Empirical variables (other than actual plasma insulin response) which were analysed included the Insulinogenic Index $\left(\frac{\Delta \text{ insulin}}{\Delta \text{ glucose}}\right)$, Area under the plasma insulin curve (Insulin Area), ratio fasting insulin/glucose, ratio post load insulin/glucose; ratio post load insulin/fasting insulin.

When the Total study group was compared to the Control group, the mean fasting (0 min) plasma insulin was similar in both groups; the mean 2-hr (120 minutes) level was significantly higher in the study group 111.84 ± 7.85 μu/ml compared to the Control group 74.01 ± 7.31 μu/ml, p=0.005. During OGTT, a pattern of delayed insulin response was demonstrated, with maximal levels being achieved at 90, and 120 minutes. The Mean Insulinogenic Index was significantly lower in the Study group compared to the Control group at all points during OGTT, except at 15 minutes (p=0.0004, p=0.0001, p=0.0003, p=0.01 at 30, 60, 90 and 120 minutes). The Mean Insuin Area was significantly lower in

the Study group 166.67 ± 10.6 μu/ml·hr compared to the Control group 186.78 ± 13.8 μu/ml hr p=0.015. The Mean fasting insulin: glucose was significantly lower and mean 2-hr insulin: fasting insulin was significantly higher in the study group (p=0.03 and p=0.02, respectively).

When the study group was divided according to the category of glucose tolerance at Year 1, similar results were obtained. The Mean fasting plasma insulin was higher in the IGT_1 group 16.09 ± 1.66 μu/ml compared to the control group 14.11 ± 1.5 μu/ml; however the difference was not significant. The Mean 2-hr (120 minutes) plasma insulin was highest in the IGT_1 group (132 ± 12.3 μu/ml) and significantly higher compared to the Control group (74.01 ± 7.11 μu/ml) at this point p=0.0056. The pattern of insulin response during OGTT differed in the IGT_1 group compared to the Control group: the Control group exhibited a prompt increase to glucose load, maximum levels being achieved at 60 minutes with subsequent decreasing levels in concert with falling glucose levels; in the IGT_1 group, although fasting insulin levels were higher, following the glucose load, there was a delayed rise with maximal levels only being achieved at 120 minutes.

The Mean Insulinogenic Index was significantly lower in the IGT_1 group compared to the Control group, at all points during OGTT, except at 15 minutes (p=0.0029, p=0.0002, p=0.0001, p=0.0001 at 30, 60, 90 and 120 minutes, respectively). Although the Mean Insulin Area was higher in the IGT_1 group (196.87 ± 18.5 μμ/ml·hr) compared to the Control group

(186.78 ± 13.78 μμ/ml·hr), no significant difference was observed.

In the Total Study group, IGT_1 group and $Diabetes_1$ groups, no significant diference was observed between obese and non-obese subjects, for Mean Plasma Insulin or Insulinogenic Index, for any time point during OGTT. In the Control group, the Mean plasma insulin was significantly higher in the obese subjects compared to non-obese subjects at 0, 15 and 60 minutes (p=0.01, p=0.02 and p=0.04, respectively).

CHAPTER 7

ELECTROCARDIOGRAM (ECG) FINDINGS AT YEAR 1

INTRODUCTION

The electrocardiogram (ECG) has been employed in cardiovascular epidemiology (Rose G and Blackburn H 1968, 1982) because:

(i) It is useful in diagnosing manifestations of ischaemic heart disease - i.e., myocardial infarction and ischaemia.

(ii) It is of value in establishing categories at risk for future cardiac events and mortality.

(iii) ECG findings are additional to, and independent of, that obtained by other methods, including medical history and physical examination.

(iv) It is an objective, quantitative record.

Classification of ECG findings by way of the Minnesota Code provides a framework for uniform reporting of ECG items.

The importance of certain Minnesota-coded ECG items as independent risk factors for subsequent mortality has been clearly shown in prospective studies of non-diabetic populations (Rose et al 1978, Prineas and Blackburn 1977). An increased prevalence of defined ECG abnormalities (based on Whitehall or US Pooling Project criteria) has also been shown in IGT subjects in the International Collaborative Groups Studies (Stamler R and Stamler J 1979).

The significance of IGT is two-fold: it is associated with an increased risk for the development of diabetes as well as macravascular disease, especially CHD. However, whether the latter risk can be "explained" on the basis of other risk factors, and the glucose intolerance is merely an innocent by-stander; or whether IGT has a more direct, pathogenic role, has been a matter of considerable debate and controversy (Jarrett RJ 1984, Bennett PH 1985, Stern et al 1985, Stamler R and Stamler J 1979).

There is substantial evidence for an increased risk of coronary heart disease (CHD) mortality among Western diabetics (West KM 1978); however the relationship between asymptomatic hyperglycaemia and CHD mortality is less consistent, as evidenced by the results of eleven prospective studies by the International Collaborative Group (Stamler R and Stamler J 1979, Fuller et al 1980).

It is commonly believed that the increased risk of cardiovascular disease, especially CHD, associated with NIDDM is due to the metabolic abnormalities of NIDDM. However, this view has been challenged (Jarrett RJ 1984, Panzram 1987) and instead an alternative hypothesis proposes that CVD and NIDDM are *associated* disorders, possibly linked genetically (Jarrett RJ 1984, Jarrett RJ and Shipley MJ 1988); the principal evidence for this being the absence of an association between the duration of diabetes and the risk of CVD, in contrast to the demonstrable and consistently strong correlation between the duration of diabetes and microvascular disease, especially diabetic retinopathy.

What is the evidence that IGT, which has an increased risk for the development of diabetes, shares a similar risk as NIDDM for CHD, but NOT for microangiopathy? The similarity in cardiovascular risk between IGT and NIDDM was reviewed by Jarrett (1984): it is well known that diabetes is associated with an increased risk of CHD and a greater degree of coronary atherosclerosis (Jarrett et al 1982, Ganda Om P 1980) and therefore it was generally felt that this was due to a greater frequency of "risk factors" common to diabetic and non-diabetic subjects viz. hypertension and lipid, haemostatic and ECG abnormalities, smoking and obesity. Compared to age matched controls, IGT subjects have been reported to have higher average blood pressure (Jarrett et al 1978), higher cholesterol (Yano et al 1982, Ostrander et al 1980), higher frequency of ECG abnormalities (Fuller et al 1980, Yano et al 1982, Keen et al 1965, Stamler R and Stamler J 1979); some prospective studies have found an increased morbidity and mortality rates from CHD in IGT subjects (Stamler R and Stamler J 1979). Moreover, intercorrelations have been demonstrated between blood glucose, blood pressure and insulin levels, the latter being found to be an independent predictor for CHD in IGT (Pyorala et al 1982, Ducimetre et al 1982). Thus IGT and NIDDM appear to share similar clinical and metabolic characteristic that confer an increased risk for CHD.

Based on these findings, Jarrett (1984) argued that diabetes is itself *NOT* a cause of CHD, but rather that atherosclerosis (and therefore clinical CHD) and diabetes *SHARE* a number of common antecedents.

The constellation of abnormalities associated with IGT (viz hypertension, obesity, hyperlipidaemia, hyperinsulinaemia) may contribute to the development of both diabetes and atherosclerosis/CHD - the extent to which each of these abnormalities is an independent contributor to CVD is difficult to ascertain, but it has even been suggested that the increased risk of CHD among diabetic subjects may be due to the fact that diabetes develops in individuals who already possess characteristics that increase the risk of CHD as well (Bennett PH 1985, Bogardus et al 1984).

As regards ECG abnormalities and IGT, an increased prevalence of ECG abnormalities has been shown in IGT subjects in most of the fifteen population studies which constituted the International Collaborative Group Study, using either the Whitehall or US Pooling Project criteria for ECG abnormalities indicative of ischaemia. However, only five of these studies showed significant associations between blood glucose and ECG abnormalities; moreover, there were inconsistent findings regarding an increase in CHD mortality with IGT. (Stamler R and Stamler J 1979).

In the Whitehall study, CHD mortality was almost doubled for subjects with IGT, within which group age, systolic blood pressure and ECG abnormalities were significantly predictive of subsequent CHD mortality.

This chapter investigates coronary heart disease (CHD) in the study group at Year 1, based on resting ECG findings employing the Minnesota code, identification of ECG abnormalities indicative of ischaemia based on Whitehall criteria, and the association of ECG abnormalities with other known risk factors for CHD.

SUBJECTS AND METHODS

SUBJECTS

The study group comprised 128 Indian subjects (67 males and 61 females) who were previously diagnosed as IGT (as described in Chapter 2 - 4).

64 Indian subjects (31 males and 33 females) who were matched for age, sex and BMI, served as controls for the study (as described in Chapter 2 and 3b).

METHODS

1) At Year 1, a 75G OGTT was performed after an overnight fast on all the subjects (as described in Chapter 2).

   According to the results of the OGTT at Year 1, the study subjects were further classified into 3 categories of glucose tolerance viz IGT_1 $Diabetes_1$ $Normal_1$.

2) At Year 1, a resting 12 lead electrocardiogram (ECG) was performed on all subjects. (A) ECG findings were reported according to the Minnesota code. (Rose G and Blackburn H 1968, 1982). (B) Using specific Minnesota code items, ECG findings were classified as "NORMAL" or "ABNORMAL" (indicative of ischaemia), based on WHITEHALL criteria (Reid et al 1974, Jarret

et al 1982, Fuller et al 1980).

(A) ECG processing was undertaken by the WHO collaborating Centre (University of London). Minnesota Coding of ECG's was performed independently, and in duplicate, by trained observers; where necessary, the discrepancies were adjusted by a third independent adjudicator.

(B) Individual Minnesota Code results were grouped into three categories:

(i) *PROBABLE ISCHAEMIA* (codes 1.1, 1.2, 7.1),
(i.e. Major Q and QS items, left bundle branch block)

(ii) *POSSIBLE/BORDERLINE ISCHAEMIA* (codes 1.3, 4.1, 4.2, 4.3, 5.1, 5.2, 5.3)
(i.e. minor Q and QS items, S-T/T Items)

(iii) *NORMAL/ISCHAEMIA UNLIKELY* (all other code items).

The classification of an "ABNORMAL" ECG (indicative of IHD) was based on the Whitehall criteria which is defined as one or more of the Minnesota code items in (i) or (ii).

3) The relationship of certain variables to "Abnormal" ECG, were also examined viz. age, BMI, blood pressure, plasma glucose, lipids, insulin and uric acid. The methodology for these have been previously described (Chapter 2).

4) The prevalence of selected risk factors were related to the presence or absence of ischaemic ECG abnormalities viz. hypertension, obesity, smoking history, hypercholesterolaemia, hypertriglyceridemia, ↓ HDL-cholesterol, hyperuricaemia.

RESULTS

Results summarised in Table 1 - 12

The results have been reported under the following:

I Prevalence of Abnormal ECG Findings (Specific Minnesota Code items indicative of IHD).

II Prevalence of IHD as indicated by "Abnormal" ECG.

III Relationship of Mean variables to "Abnormal" ECG.

IV Prevalence of selected risk factors in relation to "Abnormal" ECG.

I Prevalence of specific Abnormal ECG findings

Table 1 and 2

(a) Total Study Group:

The prevalence of major Q and QS items (1.2,1.2) was low in both the study group (6.3%) and control group (6.3%)

T-wave items (5.2 and 5.3) were the most prevalent specific abnormal ECG findings in both the study group (11.7% and 16.4%) and the control group (6.3% and 9.4%)

The prevalence of specific abnormal ECG findings (total) was higher in the study group (47.7%) then in the control group (31.3%).

TABLE 1

PREVALENCE (%) OF SPECIFIC ABNORMAL ELECTROCARDIOGRAPHIC FINDINGS (MINNESOTA CODE ITEMS) AT YEAR 1: STUDY GROUP AND CONTROL GROUP

*ELECTROCARDIOGRAPHIC ABNORMALITY (Minnesota Code Item)	Prevalence (%) Of Abnormality			
	STUDY GROUP (n=128)		CONTROL GROUP (n=64)	
	n	%	n	%
PROBABLE ISCHAEMIC HEART DISEASE				
1.1 Q and QS findings	3	2.3	2	3.1
1.2 Q and QS findings	5	3.9	2	3.1
7.1 Left bundle branch block	-	-	-	-
any "probable" finding (Total)	8	**6.3**	4	**6.3**
POSSIBLE ISCHAEMIC HEART DISEASE				
1.3 Q and QS findings	6	4.7	2	3.1
4.1 ST depression	3	2.3	-	-
4.2 ST depression	1	0.8	3	4.7
4.3 ST depression	6	4.7	1	1.6
5.1 T findings	1	0.8	-	-
5.2 T findings	15	11.7	4	6.3
5.3 T findings	21	16.4	6	9.4
any "possible finding" (Total)	53	**41.4**	16	**25.0**
POSSIBLE + PROBABLE (Total)	61	**47.7**	20	**31.3**

*Subject may have more than one abnormal finding

TABLE 2

PREVALENCE (%) OF SPECIFIC ABNORMAL ELECTROCARDIOGRAPHIC FINDINGS (MINNESOTA CODE ITEMS) AT YEAR 1: STUDY GROUP BASED ON THE CATEGORY OF GLUCOSE TOLERANCE

*ELECTROCARDIOGRAPHIC ABNORMALITY (Minnesota Code Item)	Prevalence (%) Of Abnormality		
	Category Of Glucose Tolerance		
	IGT_1 (n=47)	$DIABETES_1$ (n=41)	$NORMAL_1$ (n=40)
PROBABLE ISHAEMIC HEART DISEASE			
1.1 Q and QS finding	-	2.4	5.0
1.2 Q and QS finding	8.5	-	2.5
7.1 Left bundle branch block	-	-	-
any "probable" finding (Total)	8.5	2.4	7.5
POSSIBLE ISCHAEMIC HEART DISEASE			
1.3 Q and QS finding	4.3	7.3	2.5
4.1 ST depression	6.4	-	-
4.2 ST depression	-	-	2.5
4.3 ST depression	8.5	2.4	2.5
5.1 T wave finding	2.1	-	-
5.2 T wave finding	12.8	4.9	17.5
5.3 T wave finding	17.0	24.4	7.5
any "possible finding (Total)	51.1	39.0	32.5
POSSIBLE + PROBABLE (TOTAL)	59.6	41.5	40.0

*One subject may have one or more findings

(b) Study group based on category of glucose tolerance:

The prevalence of major Q and QS items (1.2 and 1.2) was 8.5% in the IGT_1 group, 2.4% in the $Diabetes_1$ group and 7.5% in the $Normal_1$ group.

T-wave items (5.2 and 5.3) were the most prevalent specific abnormal ECG findings in each of the three groups.

The prevalence of specific code items (total) was highest in the IGT_1 group (59.6%).

II Prevalence of IHD as indicated by "Abnormal" ECG:

Table 3 and 4

(a) Total study group:

The prevalence of "Abnormal" ECG was higher in the study group (35.2%) compared to the control group (21.9%); however the difference was not significant (p=0.06). "Possible" IHD was the commoner of the two ECG abnormalities in both the study group (28.9%) and the control group (15.6%).

In both the study and control groups, the prevalence of "Abnormal" ECG was higher in females (44.3% and 30.3%, respectively) than in males (26.9% and 12.9%, respectively), contributed to by the higher prevalence of "Possible" IHD in females.

TABLE 3

PREVALENCE (%) OF ISCHAEMIC HEART DISEASE AT YEAR 1, AS INDICATED BY "ABNORMAL ELECTROCARDIOGRAM (ECG)"+: STUDY GROUP AND CONTROL GROUP

GROUP (number examined)	ABNORMAL ECG					
	POSSIBLE		PROBABLE		°POS OR PROB	
	n	%	n	%	n	%
IGT_1 (47)	15	31.9	4	8.5	19	40.4*
$DIABETES_1$ (41)	13	31.7	1	2.4	14	34.2
$NORMAL_1$ (40)	9	22.5	3	7.5	12	30.0
TOTAL STUDY GROUP (128)	37	28.9	8	6.3	45	35.2**
CONTROL GROUP (64)	10	15.6	4	6.3	14	21.9

+"Abnormal ECG" as based on Whitehall Criteria i.e. "Possible" or "Probable"
°Pos = "possible" ischaemic heart disease (Minnesota codes 1.3, 4.1-3, 5.1-3)
Prob = "probable" ischaemic heart disease (Minnesota codes 1.1, 1.2, 7.1)
* p=0.035 IGT1 vs Control
**p=0.06 Total Study Group vs Control

TABLE 4

PREVALENCE (%) OF ISCHAEMIC HEART DISEASE AS INDICATED BY *"ABNORMAL ELECTROCARDIOGRAM (ECG)" IN THE STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE: SEX DISTRIBUTION

GROUP (number examined)	ABNORMAL ECG					
	POSSIBLE		PROBABLE		+POS OR PROB	
	n	%	n	%	n	%
IGT_1						
male (28)	6	21.4	3	10.7	9	32.1
female (19)	9	47.4	1	5.3	10	52.6
$DIABETES_1$						
male (15)	2	13.3	1	6.7	3	20.0
female (26)	11	42.3	-	-	11	42.3
$NORMAL_1$						
male (24)	3	12.5	3	12.5	6	25.0
female (16)	6	37.5	-	-	6	37.5
TOTAL STUDY GROUP						
male (67)	11	16.4	7	10.5	18	26.9
female (61)	26	42.6	1	1.6	27	44.3
CONTROL GROUP						
male (31)	3	9.7	1	3.2	4	12.9
female (33)	7	21.2	3	9.1	10	30.3

*"Abnormal" ECG as based on Whitehall Criteria i.e. "Possible" or "Probable"

+ Pos=possible ischaemic heart disease (Minnesota codes 1.3, 4.1-3, 5.1-3)
  Prob=probable ischaemic heart disease (Minnesota codes 1.1, 1.2, 7.1)

(b) Study group based on category of glucose tolerance:

The prevalence of "Abnormal" ECG was highest in the IGT_1 group (40.4%), being significantly higher compared to the control group (21.9%) P=0.035. 34.2% of the $Diabetes_1$ group, and 30% of the $Normal_1$ group had "Abnormal" ECG. In all groups, "Possible" IHD was the more prevalent ECG abnormality.

As regards sex distribution, the prevalence of "Abnormal" ECG was higher in females than in males, for each of the three study groups. The prevalence of "Possible" IHD was higher in females than in males, whilst that of "Probable" IHD was higher in males than in females, for each of the three study groups.

III Relationship of mean variables to "Abnormal" ECG:

Table 5 - 9

(a) Total study group:

Table 5 and 6

In the study group, of all the variables examined, only the Mean Age was significantly higher in those subjects with "Abnormal" ECG, 54.8 years, compared to those with "Normal" ECG, 45.1 years, $p<0.0001$. In the control group, mean systolic and diastolic blood pressure were significantly higher in the subjects with "Abnormal" ECG (p=0.03 and 0.046, respectively).

TABLE 5

RELATIONSHIP OF MEAN VARIABLES TO "ABNORMAL ECG" AT YEAR 1:
STUDY GROUP AND CONTROL GROUP

VARIABLE	STUDY GROUP			CONTROL GROUP		
	ECG Abnormal (n=45)	ECG Normal (n=83)		ECG Abnormal (n=14)	ECG Normal (n=50)	
Age (years)	54.8	45.1	***	44.6	41.9	-
BMI (Kg/m^2)	26.5	25.5	-	25.7	23.9	-
Blood pressure (mmHg):						
Systolic	134.4	127.5	-	126.4	114.0	*
Diastolic	84.3	79.8	-	78.6	72.2	*
Plasma cholesterol (mmol/L)	6.6	6.3	-	6.0	5.97	-
Plasma triglyceride (mmol/L)	2.3	2.2	-	1.5	1.5	-
Plasma HDL-cholesterol(mmol/L)	1.4	1.1	-	1.2	1.2	-
Plasma uric acid (mmol/L)	0.39	0.34	-	0.31	0.35	-
Plasma glucose (mmol/L):						
Fasting	6.4	6.5	-	5.5	5.4	-
2-hr	10.3	9.9	-	5.5	5.1	-
Plasma insulin (μu/ml):						
Fasting	12.9	15.1	-	14.9	14.5	-
2-hr	116.0	109.6	-	67.3	77.0	-

* $p < 0.05$
*** $p < 0.0001$
\- p not significant

Table 6

RELATIONSHIP OF MEAN VARIABLES TO "ABNORMAL ECG" IN STUDY GROUP AND CONTROL GROUP AT YEAR 1: SEX DISTRIBUTION

+ VARIABLE	STUDY GROUP						CONTROL GROUP					
	FEMALES			MALES			FEMALES			MALES		
	ECG Abnormal (n=27)	ECG Normal (n=34)		ECG Abnormal (n=18)	ECG Normal (n=49)		ECG Abnormal (n=10)	ECG Normal (n=23)		ECG Abnormal (n=4)	ECG Normal (n=27)	
Age	53.9	44.1	**	56.0	45.8	**	45.4	40.6	-	42.5	42.8	-
BMI	27.7	26.3	-	24.7	24.9	-	27.1	24.4	-	20.9	23.5	-
Systolic BP	135.6	127.7	-	132.8	127.4	-	129.0	107.1	**	120.0	118.97	-
Diastolic BP	85.2	78.4	-	83.1	80.8	-	80.0	67.6	**	75.0	75.5	-
Plasma chol	6.8	6.0	*	6.4	6.5	-	6.2	5.5	-	5.7	6.3	-
Plasma Tg	2.1	1.7	-	2.5	2.5	-	1.5	1.1	-	1.5	1.8	-
Plasma HDL-chol	1.2	1.2	-	1.6	1.0	-	1.3	1.3	-	1.1	1.1	-
Plasma uric acid	0.36	0.30	**	0.44	0.37	-	0.29	0.29	-	0.35	0.39	-
Plasma glucose:												
fasting	6.4	6.7	-	6.4	6.4	-	5.6	5.2	-	5.3	5.5	-
2-hr	10.7	10.8	-	9.7	9.2	-	5.5	4.97	-	5.6	5.3	-
Plasma insulin:												
fasting	13.9	13.3	-	11.4	16.3	-	17.6	14.3	-	8.2	14.7	-
2-hr	113.7	107.8	-	119.5	110.8	-	64.7	77.0	-	73.0	77.1	-

+ See Table 5 for details on variables

* $p < 0.05$

** $p < 0.01$

\- p not significant

When the sexes were examined separately (Table 6), the results were as follows: in the study group, for females, the Mean Age, serum total cholesterol and serum uric acid were significantly higher in subjects with "Abnormal" ECG compared to those with "Normal" ECG (p0.002, p0.02, p0.007); for males in the study group, the Mean Age was significantly elevated in those with "Abnormal" ECG (p=0.002). In the control group, for females, the Mean systolic and diastolic blood pressure was significantly higher in subjects with "Abnormal" ECG compared to those with "Normal" ECG (p=0.004)

(b) <u>Study group based on category of glucose tolerance:</u>

Table 7 - 9

For each of the three groups (IGT_1 $Diabetes_1$ $Normal_1$), the Mean Age was significantly elevated in subjects with "Abnormal" ECG compared to those with "Normal" ECG. Of the remaining variables analysed, Mean 2-hr plasma glucose (IGT_1 group only) was significantly elevated in those subjects with "Abnormal" ECG; Mean fasting insulin ($Normal_1$ group only) was significantly decreased in subjects with "Abnormal" ECG.

When the sexes were examined separately, the results were as follows: for males, Mean Age ($Normal_1$ group only), Serum HDL-cholesterol ($Diabetes_1$ group only) and 2-hr plasma glucose (IGT_1 group only), were significantly elevated in those subjects with "Abnormal" ECG; for females, the Mean Age (IGT_1 and $Normal_1$ groups), serum cholesterol ($Normal_1$ group only), serum uric acid

Table 7

RELATIONSHIP OF MEAN VARIABLES TO "ABNORMAL ECG" : STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

+VARIABLE	CATEGORY OF GLUCOSE TOLERANCE								
	IGT$_1$			DIABETES$_1$			NORMAL$_1$		
	ECG Abnormal (n=19)	ECG Normal (n=28)		ECG Abnormal (n=14)	ECG Normal (n=27)		ECG Abnormal (n=12)	ECG Normal (n=28)	
Age	52.6	45.7	*	57.6	48.4	*	54.9	41.3	**
BMI	26.4	25.2	-	28.2	27.2	-	24.9	24.0	-
Systolic BP	135.3	126.8	-	137.1	132.96	-	130.0	122.9	-
Diastolic BP	86.1	79.1	-	85.0	83.3	-	80.8	77.1	-
Plasma chol	6.5	6.6	-	6.9	6.5	-	6.6	5.9	-
Plasma Tg	2.1	1.8	-	2.6	2.9	-	2.1	1.9	-
Plasma HDL-chol	1.6	1.1	-	1.2	1.1	-	1.2	1.1	-
Plasma uric acid	0.39	0.34	-	0.38	0.34	-	0.42	0.34	-
Plasma glucose:									
fasting	6.3	6.3	-	7.7	8.0	-	5.3	5.3	-
2-hr	9.9	9.0	**	14.7	14.7	-	5.7	6.1	-
Plasma insulin:									
fasting	17.4	15.2	-	12.4	18.4	-	6.3	11.7	-
2-hr	135.6	129.6	-	95.1	107.6	-	109.3	91.5	-

+ See Table 5 for details on variable

* $p < 0.05$

** $p < 0.01$

- p not significant

Table 8

RELATIONSHIP OF MEAN VARIABLE TO "ABNORMAL ECG" : STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1 (MALES)

+ VARIABLE	CATEGORY OF GLUCOSE TOLERANCE								
	IGT_1			$DIABETES_1$			$NORMAL_1$		
	ECG Abnormal (n=9)	ECG Normal (n=19)		ECG Abnormal (n=3)	ECG Normal (n=12)		ECG Abnormal (n=6)	ECG Normal (n=18)	
Age	52.3	46.1	-	62.0	49.3	-	58.5	43.1	*
BMI	24.6	24.9	-	25.2	26.7	-	24.6	23.6	-
Systolic BP	136.7	128.4	-	130.0	130.0	-	128.3	124.4	-
Diastolic BP	83.9	80.0	-	86.7	84.2	-	80.0	79.4	-
Plasma chol	6.5	6.9	-	7.1	6.5	-	5.8	6.1	-
Plasma Tg	2.5	1.9	-	2.1	3.9	-	2.9	2.2	-
Plasma HDL-chol	2.1	1.0	-	1.2	0.97	**	1.1	1.1	-
Plasma uric acid	0.41	0.36	-	0.30	0.37	-	0.55	0.36	-
Plasma glucose:									
fasting	6.3	6.4	-	8.97	8.2	-	5.3	5.3	-
2-hr	9.8	8.99	*	16.8	14.5	-	5.95	5.9	-
Plasma insulin									
fasting	14.9	16.9	-	12.2	22.1	-	5.8	11.9	-
2-hr	122.9	135.8	-	68.2	97.1	-	140.1	93.40	-

+ See Table 5 for details on variables

* $p < 0.05$

** $p < 0.01$

- p not significant

Table 9

RELATIONSHIP OF MEAN VARIABLES TO "ABNORMAL ECG" : STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1 (FEMALES)

+ VARIABLE	IGT_1			$DIABETES_1$			$NORMAL_1$		
	ECG Abnormal (n=10)	ECG Normal (n=9)		ECG Abnormal (n=11)	ECG Normal (n=15)		ECG Abnormal (n=6)	ECG Normal (n=10)	
Age	52.8	44.8	*	56.4	47.8	-	51.3	37.9	*
BMI	27.9	25.9	-	28.98	27.7	-	25.1	24.8	-
Systolic BP	134.0	123.3	-	139.1	135.3	-	131.7	120.0	-
Diastolic BP	88.0	77.1	-	84.6	82.7	-	81.7	73.0	-
Plasma chol	6.4	6.0	-	6.8	6.4	-	7.4	5.5	**
Plasma Tg	1.8	1.5	-	2.7	2.1	-	1.4	1.4	-
Plasma HDL-chol	1.2	1.2	-	1.2	1.2	-	1.4	1.3	-
Plasma uric acid	0.37	0.29	*	0.4	0.31	*	0.29	0.30	-
Plasma glucose:									
fasting	6.2	6.1	-	7.3	7.8	-	5.2	5.5	-
2-hr	9.98	9.1	*	14.2	14.8	-	5.4	6.4	-
Plasma insulin:									
fasting	19.6	11.8	-	12.5	15.4	-	6.8	11.4	-
2-hr	147.0	116.4	-	102.5	115.8	-	78.6	88.0	-

+ See Table 5 for details on variables

* $p < 0.05$

** $p < 0.01$

- p not significant

(IGT_1 and $Diabetes_1$ groups) and 2-hr plasma glucose (IGT_1 group only), were significantly elevated in those subjects with "Abnormal" ECG.

IV Prevalence of selected risk factors in relation to "Abnormal" ECG

Table 10 - 12

(a) Total study group:

Table 10 and 11

In the study group, the prevalence of obesity and hyperuricaemia was significantly higher in those subjects with "Abnormal" ECG, compared to those with "Normal" ECG ($p=0.03$ and <0.0001, respectively); the prevalence of smoking history was significantly lower in those with "Abnormal" ECG ($p=0.02$). In the control group, hyperuricaemia was more prevalent in subjects with "Abnormal" ECG ($p=0.04$).

In the study group, for males, the prevalence of hyperuricaemia was significantly higher in subjects with "Abnormal" ECG; whilst for females, that of hypertension, obesity, hypercholesterolaemia (chol $\geq$ 6.5 mmol/L) and hyperuricaemia were significantly higher in those subjects with "Abnormal" ECG compared to those with "Normal" ECG. In the control group, for females, the prevalence of hypercholesterolaemia (chol $\geq$ 6.5mmol/L) and hypertriglyceridaemia ($\geq$ 2.0 mmol/L) was significantly higher in those subjects with "Abnormal" ECG.

Table 10

PREVALENCE OF SELECTED RISK FACTOR IN RELATION TO PRESENCE OR ABSENCE OF ELECTROCARDIOGRAPHIC ABNORMALITIES ("ABNORMAL" ECG) : STUDY GROUP AND CONTROL GROUP AT YEAR 1

RISK FACTOR	STUDY GROUP Prevalence (%)			CONTROL GROUP Prevalence (%)		
	ECG Abnormal (n=45)	ECG Normal (n=83)		ECG Abnormal (n=14)	ECG Normal (n=50)	
+ Hypertension	24.4	13.3	-	7.1	4.0	-
+ Obesity	54.6	34.9	*	53.9	27.7	-
Smoking (current)	20.0	40.7	*	21.4	24.0	-
Hypercholesterolaemia :						
$\geq$ 6.5 mmol/L	53.3	37.4	-	35.7	30.0	-
$\geq$ 5.7 mmol/L	73.3	65.1	-	50.0	62.0	-
Hypertriglyceridaemia :						
$\geq$ 2.0 mmol/L	44.4	33.7	-	28.6	22.0	-
$\geq$ 1.7 mmol/L	55.6	48.2	-	28.6	28.0	-
↓ HDL-cholesterol						
($<$ 0.9 mmol/L)	13.3	10.8	-	14.3	16.0	-
Hyperuricaemia :	46.7	14.5	***	35.7	12.0	*
($\geq$ 0.42 males)						
($\geq$ 0.36 females)						

+ Hypertension : BP $\geq$ 160 and/or mmHg $\geq$ 95

Obesity : BMI $\geq$ 27 in males, $\geq$ 25 in females

* $p < 0.05$

*** $p < 0.0001$

\- p not significant

Table 11

PREVALENCE OF SELECTED RISK FACTORS IN RELATION TO ELECTROCARDIOGRAPHIC ABNORMALITIES ("ABNORMAL ECG") AT YEAR 1 : SEX DISTRIBUTION IN THE STUDY GROUP AND CONTROL GROUP

RISK FACTOR	STUDY GROUP						CONTROL GROUP					
	MALES Prevalence (%)			FEMALES Prevalence (%)			MALES Prevalence (%)			FEMALES Prevalence (%)		
	ECG Abnormal (n=18)	ECG Normal (n=49)		ECG Abnormal (n=27)	ECG Normal (n=34)		ECG Abnormal (n=4)	ECG Normal (n=27)		ECG Abnormal (n=10)	ECG Normal (n=23)	
+ Hypertension	11.1	16.3	-	33.3	8.8	*	0.0	3.5	-	10.0	4.8	-
+ Obesity	27.8	26.5	-	73.1	47.1	*	0.0	11.1	-	70.0	50.0	-
Smoking (current)	38.9	55.3	-	7.4	20.6	-	50.0	27.6	-	10.0	19.1	-
Hypercholesterolaemia:												
≥ 6.5 mmol/L	44.4	42.9	-	59.3	29.4	*	25.0	44.8	-	40.0	9.52	*
≥ 5.7 mmol/L	66.7	69.4	-	77.8	58.8	-	25.0	75.9	*	60.0	42.9	-
Hypertriglyceridaemia:												
≥ 2.0 mmol/L	61.1	40.8	-	33.3	23.5	-	25.0	37.9	-	30.0	0.0	**
≥ 1.7 mmol/L	61.1	55.1	-	51.9	38.9	-	25.0	44.8	-	30.0	4.8	-
↓ HDL-cholesterol (< 0.9 mmol/L)	11.1	14.3	-	14.8	5.9	-	25.0	27.6	-	10.0	0.0	-
Hyperuricaemia:	38.9	12.2	*	51.9	17.7	**	50.0	17.2	-	30.0	4.8	-

+ Hypertension : BP ≥ 160 and/or mmHg
≥ 95

Obesity : BMI ≥ 27 in males
≥ 25 in females

* $p < 0.05$
** $p < 0.01$
- p not significant

(b) Study group based on category of glucose tolerance:

Table 12

In the IGT_1 and $Diabetes_1$ groups, the prevalence of hyperuricaemia was significantly higher in those subjects with "Abnormal" ECG compared to those with "Normal" ECG (52.6% vs 7.1% in IGT_1 group, and 57.1% vs 25.9% in $Diabetes_1$ group; $p<0.0001$ and 0.049, respectively). In the $Diabetes_1$ and $Normal_1$ groups, the prevalence of smoking history was significantly lower in those subjects with "Abnormal" ECG.

Table 12

PREVALENCE OF SELECTED RISK FACTORS IN RELATION TO ELECTROCARDIOGRAPHIC ABNORMALITIES ("ABNORMAL" ECG) AT YEAR 1 : STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE

RISK FACTOR	CATEGORY OF GLUCOSE TOLERANCE								
	IGT_1 Prevalence (%)			$DIABETES_1$ Prevalence (%)			$NORMAL_1$ Prevalence (%)		
	ECG Abnormal (n=19)	ECG Normal (n=28)		ECG Abnormal (n=14)	ECG Normal (n=27)		ECG Abnormal (n=12)	ECG Normal (n=28)	
+ Hypertension	21.1	10.7	-	42.9	18.5	-	8.3	10.7	-
+ Obesity	57.9	32.1	-	61.5	44.4	-	41.7	28.6	-
Smoking (current)	31.6	25.9	-	7.1	44.4	*	16.7	51.9	*
Hypercholesterolaemia:									
≥ 6.5 mmol/L	42.1	39.3	-	64.3	37.0	-	58.3	35.7	-
≥ 5.7 mmol/L	78.95	67.9	-	71.4	77.8	-	66.7	50.0	-
Hypertriglyceridaemia:									
≥ 2.0 mmol/L	47.4	21.4	0.06	57.1	55.6	-	25.0	25.0	-
≥ 1.7 mmol/L	68.4	39.3	0.05	64.3	70.4	-	25.0	35.7	-
↓ HDL-cholesterol (<0.9mmol/L)	15.8	14.3	-	14.3	11.1	-	8.3	7.1	-
Hyperuricaemia (≥ 0.42 males) (≥ 0.36 females)	52.6	7.1	***	57.1	25.9	*	25.0	10.7	-

+ Hypertension: BP ≥160 and/or mmHg
≥ 95

Obesity: BMI ≥27 in males
≥25 in females

* p < 0.05
*** p < 0.001
- p not significant

DISCUSSION

The significance of IGT lies in its association with an increased risk for the development of diabetes mellitus and macrovascular disease, especially coronary heart disease (CHD) (NDDG 1979, WHO 1980, 1985, Fuller et al 1980, Keen et al 1965). However, whether the latter risk can be "explained" on the basis of other risk factors with the glucose intolerance being merely an "innocent bystander", or whether IGT has a more direct pathogenic role, has been a matter of considerable debate and controversy (Jarrett RJ 1984, Bennett PH 1985, Stern et al 1985, Stamler R and Stamler J 1979).

The electrocardiogram (ECG) has been employed in cardiovascular epidemiology not only for diagnosing manifestations of IHD, but also for establishing categories at risk for future cardiac events and mortality; it is an adjunct to, and an independent assessment obtained by other methods viz history and physical examination (Rose et al 1968, 1982). Other risk factors for CHD/IHD include blood pressure; glucose, lipid, insulin and haemostatic abnormalities; smoking, age and obesity (Jarrett RJ 1984).

Therefore, to evaluate CHD in IGT, it would be important to examine the prevalence of CHD by way of ECG abnormalities, to study the relationship of such ECG abnormalities with other known risk factors associated with CHD, and ultimately to assess whether an increased CHD morbidity and mortality is associated with IGT.

As regards the prevalence of ECG abnormalities in IGT, the classification of ECG findings, by way of the Minnesota code, provides a framework for uniform reporting of ECG items (Rose et al 1968, 1982). The importance of certain Minnesota-coded ECG items as independent risk factors for subsequent CHD mortality, has been clearly shown in prospective studies of non-diabetic populations (Rose et al 1978, Prineas RJ and Blackburn H 1977). An increased prevalence of defined ECG abnormalities using Whitehall or US Pooling Project criteria has also been demonstrated in IGT subjects, in most of the fifteen prospective population studies which constituted the International Collaborative Group (Stamler R and Stamler J 1979); other studies have also shown an increased prevalence of ECG abnormalities in IGT subjects, either in cross-sectional studies (Keen et al 1965, Ostrander et al 1965), or as part of prospective studies (Fuller et al 1980, Yano et al 1982, Jarret etal 1982). Two of these quoted studies deserve comment.

The Bedford Survey (Keen et al 1965) was undertaken to examine whether an increased tendency to arterial disease (as evidenced by symptoms and ECG changes) was associated with hyperglycaemia, whether due to diabetes or "borderline" hyperglycaemia. Of 501 subjects studied, 104 were diabetic, 210 "borderline" hyperglycaemia, and 187 had Normal glucose tolerance. The age-adjusted prevalence of both symptoms and ECG changes of CHD was lowest in the Control group, intermediate in the borderline group and highest in the diabetics. With respect to the ECG changes, the prevalence of Q/QS items ("Probable" ischaemia) was low in all three groups, whilst that of ST/T items ("Possible" ischaemia) was higher in all three groups, and showed clear gradations with increasing glucose tolerance, and in both sexes. When the sexes were compared, only the prevalence of Q/QS items ("Probable" ischaemia) was higher in males compared to females, whilst the prevalence of ST/T items ("Possible" ischaemia) and symptoms, was higher in females for each of the three groups. In that study, it was questioned whether the high prevalence of ST/T items was related to hypertension; however, even when controlled for blood pressure, there was a clear gradient of ECG changes with increasing blood glucose levels. The demonstration that ECG changes and symptoms were commoner in females was surprising, since it had been generally supposed that IHD was commoner in males; the explanation for this paradox was that fewer of the women affected by CHD die of the disease - which was consistent with the lower rate, in women, of Q/QS change, ("Probable" ischaemia) (which is the most specific index of myocardial ischaemia), since this is an index of the frequency of the lethal form of the disease. The above study was important, since it was one of the first studies which examined the relationship between "borderline" hyperglycaemia and CHD; moreover, it is one of the few studies on IGT and CHD, in which both sexes were studied.

Undoubtedly, the widest quoted reference with respect to cardiovascular disease and glucose intolerance is the Whitehall study, which has been a prospective investigation of cardio-respiratory disease in over 18,000 male civil servants in London since 1967, and from which emerged the widely used "Whitehall" criteria for ECG abnormalities of ischaemia (Reid et al 1974, 1976, Fuller et al 1979, 1980, 1983, Stamler R and Stamler J 1979, Jarret RJ and Shipley MJ 1988). In the study which examined CHD risk and IGT (Fuller et al 1980), subjects were divided according to category of glucose tolerance (N, IGT, Diabetes), and the conclusion was that the prevalence of ECG abnormalities was highest in the IGT group. With respect to specific ECG changes, there was an increased prevalence in the IGT compared to Normal group, of ST/T items ("Possible Ischaemia") and left bundle-branch block (7.1); however the prevalence of Q/QS items ("Probable Ischaemia"), although higher in the IGT than Normal group, was not significantly so.

Most of the International Collaborative Group studies demonstrated an increased prevalence of defined ECG abnormalities (using Whitehall or US Pooling Project Criteria) in subjects with asymptomatic hyperglycaemia (IGT) at baseline examination, despite inconsistencies in the methods used for ascertaining hyperglycaemia (Stamler R and Stamler J 1979). Of note though, is that in those studies, as with the Whitehall Study, only male suvbjects were examined.

The finding in the present study, of a higher prevalence of Abnormal ECG in the Study group (35.2%), contributed to mainly by the higher prevalence of "Possible" ischaemia, is therefore in accordance with that found both in the Whitehall and Bedford Studies (Fuller et al 1980, Keen et al 1965). The demonstration that the prevalence of "Possible" ischaemia was higher in the study group females, whilst that of "Probable" ischaemia was higher in study group males, is in accordance with the findings in the Bedford Study (in the Whitehall

Survey, only males were examined). Of note, is that both in the present study and the Bedford study, the prevalence of "Possible" ischaemia (ST/T items) was higher in females compared to males. It has been suggested that in females, the significance of ST/T abnormalities as detected by the Minnesota code is questionable, as it may reflect physiological rather than pathological difference, and that the increased prevalence may be more apparent than real. However, a pointer against this suggestion is the finding that even in the Whitehall study (in which only males were examined) the prevalence of ST/T ("Possible" ischaemia) items was higher in the IGT group, compared to the Control group; moreover in the present study, when the males were examined separately, not only was the prevalence of ST/T items ("Possible" Ischaemia) higher in study group males (16.4%) compared to males in Control group (9.7%), but also that the prevalence of ST/T items ("Possible" ischaemia) was higher than that of Q/QS items, ("Probable" ischaemia) both in study group and control males. Thus it would appear, that whether the sexes are examined separately or combined, and irrespective of category of glucose tolerance, the prevalence of ST/T items are higher than that of Q/QS items; perhaps, as put forward by Keen et al (1965), whilst IHD is commoner in males than females, there would be fewer individuals with major Q items (definite infarct) who would survive, and it is only those with lesser degrees of ischaemia who actually survive, and therefore be available for examination.

It is important to note that the above comparisons between the present and other quoted studies takes into account the Total study group;

however, although the study subjects were IGT a year previously, at the time the ECG were performed, these IGT subjects had already entered into the first year of the natural history of their IGT - and were therefore either IGT_1, $Diabetes_1$ or $Normal_1$. However, even when the study group was divided according to the category of glucose tolerance at Year 1, and compared to the Control group, the findings were much the same as when the Total study group was examined: The IGT_1 group had the highest prevalence of "Abnormal" ECG, (40.4%), the prevalence being almost twice as that in the Control group (21.9%); the rates in the $Diabetes_1$ and $Normal_1$ groups being intermediate (34.2% and 30% respectively). The prevalence of both "Possible" and "Probable" ischaemia was highest in the IGT_1 group, that of "Possible" being almost double in the IGT_1 group (32%) compared to Control group (15.6%). When the sexes were examined separately, the prevalence of "Abnormal" ECG and "Possible" ischaemia was highest in the IGT_1 group both for males and females.

Thus the findings in the present study support those of previous studies which have demonstrated a high prevalence of IHD as indicated by ECG abnormalities in subjects with IGT. Prospective studies viz. the Whitehall Study (Fuller et al 1980), have demonstrated that in IGT subjects, ECG abnormalities, systolic blood pressure and age were independent risk factors for CHD mortality; therefore, abnormalities in resting ECG may define "at risk" IGT subjects who may be suitable for intervention programmes.

The finding in the present study, of a high prevalence of IHD (as indicated by ECG abnormalities), in the Control group (21.9%) is in accordance with previously published reports on mortality data, which have demonstrated a high incidence of IHD in South African Indians (Walker ARP 1980, Wyndham et al 1982). However, to date, there are no reports of epidemiological studies evaluating CHD in South African Indians with IGT. In a hospital study of 103 South African Indian Myocardial Infarct survivors, abnormal glucose tolerance and lipid abberation were found to be significant risk factors - 55% of these patients had abnormal glucose tolerance (14% IGT, 41% Diabetes) (Sewdarsen et al 1983).

With respect to the relationship of baseline variable to ECG abnormalities, several variables were examined in the fifteen population studies constituting the International CollaborativeGroup Study viz. age, systolic blood pressure, glucose, BMI, cholesterol and smoking. A significant association was found between ECG abnormalities and the following variables - age (in 6 studies), systolic blood pressure (11studies), glucose (3 studies), cholesterol (5 studies), BMI (1 study) and cigarette smoking (1 study) (Stamler R and Stamler J 1979). However, in these studies, this analysis included all subjects irrespective of category of glucose tolerance, unlike the present study.

In the present study, when all subjects were examined irrespective of glucose tolerance (ie. study group + control group), a significant association was found between ECG abnormalities and the following variables - age, systolic and diastolic blood pressure; a surprising finding though was that HDL-cholesterol was significantly higher in subjects with "Abnormal" ECG compared to those with "Normal" ECG - the significance of this is unclear; perhaps examination of HDL-subfractions, is of greater value in this regard.

On further analysis, it was found that in the Total Study group, age (sexes combined and separately), cholesterol and uric acid (females only) were significantly elevated in subjects with "Abnormal" ECG, whilst in the Control group, systolic and diastolic blood pressure (sexes combined, females) were significantly elevated. When the Study group was divided according to the category of glucose tolerance in the IGT_1 group, age (sexes combined, females) serum uric acid (females), 2-hr glucose (sexes combined and separately) were significantly elevated in subjects with "Abnormal" ECG.

Of interest was that in the IGT_1 group, the Mean 2-hr glucose was significantly higher in subjects with "Abnormal" ECG compared to those with "Normal" ECG. Perhaps this observation may have implications in the long term, ie. if, as has been quoted above (Fuller et al 1980), ECG abnormality is a significant risk factor for subsequent CHD mortality in IGT subjects and if as in the present study IGT subjects with "Abnormal" ECG have higher 2-hr plasma glucose; then, perhaps intervention programmes in this IGT group may reduce the risk of CHD mortality in such subjects. Another interesting observation was that the Mean serum uric acid was significantly elevated in females with "Abnormal" ECG (in the Total Study Group, IGT_1 and $Diabetes_1$, Groups).

However, the significance of this finding has not yet been established.

With respect to the prevalence of other risk factors in those with "Abnormal" ECG, the finding in the Whitehall Study (Fuller et al 1980) was that CHD mortality was almost doubled for subjects with IGT_1 within which group age, systolic blood pressure, and ECG abnormalities were significantly predictive of subsequent CHD mortality. The present study has shown a high prevalence of IHD as indicated by ECG abnormalities, in both the Total study group (35%) and the IGT_1 group (40.4%), the prevalence in the latter being almost twice that in the control group. An interesting finding was that the prevalence of certain risk factors was high in those with "Abnormal" ECG viz obesity (Total study group females), hypertension (Total study group females), hyperuricaemia (Total study group females, IGT_1), hypercholesterolaemia (Total study group females). These may have therapeutic implications; therefore in subjects with IGT_1 control of weight, blood pressure, uric acid and cholesterol may be of significance in reducing CHD mortality - however, prospective studies on mortality/morbidity from CHD will be required in South African Indians with IGT.

Of interest in the present study, was that the prevalence of smoking history was lower in the study subjects with abnormal ECG - this is probably explained by the fact that fewer males than females had abnormal ECG, and that the prevalence of smoking was low in females - however, even for males the prevalence was lower in those with

"Abnormal" ECG compared to those with "Normal" ECG. Thus, in the present study, smoking does not appear to be a risk factor for CHD in IGT subjects.

In conclusion, the present study has demonstrated that in the IGT_1 group, the prevalence of IHD (as indicated by "Abnormal" ECG) is high and almost double when compared to control subjects; that the prevalence of "Abnormal" ECG was higher in females; and that "Possible" ischaemia is the commoner ECG abnormality. In the IGT_1 group, Mean age and 2-hr plasma glucose levels were significantly higher in those with "Abnormal" ECG, and in IGT_1 females, Mean serum uric acid was elevated in those with "Abnormal" ECG.

SUMMARY

Coronary heart disease (CHD) was investigated in the study group at Year 1, based on resting electrocardiogram (ECG) findings employing the Minnesota code, identification of ECG abnormalities suggestive of ischaemia based on "Whitehall" criteria, and the association of ECG abnormalities with other known risk factors for CHD. 12 - lead resting electrocardiogram (ECG) was performed on 128 study subjects (67 males and 61 females) who were diagnosed IGT a year previously, and on 64 control subjects (31 males and 33 females). Study subjects were further divided according to category of glucose tolerance at Year 1 viz IGT_1 $Normal_1$ and $Diabetes_1$.

When the study group was examined as a whole (Total Study Group), the prevalence of CHD, as indicated by "Abnormal" ECG was higher, 35.2% compared to the Control group (21.9%); however the difference fell just short of statistical significance (p=0.06). The prevalence of "Abnormal" ECG was higher in females than in males, in both groups. Of the two ECG abnormalities, "Possible" ischaemia was the more prevalent; that of "Probable" ischaemia was low, and in the study was higher in males. In the Study group (sexes combined), the Mean Age was significantly higher in those subjects with "Abnormal" ECG, compared to those with "Normal" ECG ($p<0.0001$); for females, Mean age, serum cholesterol and serum uric acid were significantly higher (p=0.002, p=0.02, p=0.007, respectively); for males, the Mean Age was significantly elevated in those subjects with "Abnormal" ECG (p=0.0002). The prevalence of obesity and hyperuricaemia was

significantly higher in study subjects (sexes combined) with "Abnormal" ECG, compared to those with "Normal" ECG ($p=0.03$, $p<0.0001$, respectvively); for females, the prevalence of hypertension, obesity, hypercholesterolaemia and hyperuricaemia were significantly higher ($p=0.017$, p=0004, $p=0.02$, $p=0.005$, respectively); for males, hyperuricaemia was more prevalent in those subjects with "Abnormal" ECG ($p=0.015$).

When the Study group was divided according to the category of glucose tolerance at Year 1 (IGT_1 $Diabetes_1$ $Normal_1$), the prevalence of IHD as indicated by "Abnormal" ECG was highest in the IGT_1 group (40.4%) and almost twice that in the Control group (21.99%), $p=0.035$; the prevalence being intermediate in the $Diabetes_1$ (34.2%) and $Normal_1$ (30%) groups. Whether the sexes were examined separately or combined, the prevalence of "Abnormal" ECG and "Possible" ischaemia was highest in the IGT_1 group; the prevalence of "Probable" ischaemia was higher in the IGT_1 group than in control group (sexes combined, males). In the IGT_1 group (sexes combined) Mean Age and 2-hr plasma glucose were significantly higher in those subjects with "Abnormal" ECG, compared to those with "Normal" ECG ($p=0.02$, $p=0.002$ respectively); for females, Mean Age, serum uric acid and 2-hr plasma glucose were significantly higher ($p=0.03$, $p=0.012$, $p=0.03$ respectively); for males, 2-hr plasma glucose was significantly elevated in those subjects with "Abnormal" ECG ($p=0.049$). The prevalence of hyperuricaemia was significantly higher in IGT_1 subjects with "Abnormal" ECG compared to those with "Normal" ECG ($p<0.0001$).

CHAPTER 8

SERUM LIPID AND LIPOPROTEIN LEVELS AT YEAR 1

INTRODUCTION

Prospective studies on subjects with IGT have highlighted an increased risk not only of progression to NIDDM but also of subsequent development of macrovascular disease.

With respect to the latter risk, a few long term studies have demonstrated an increased frequency of morbidity and mortality from macrovascular disease, especially coronary heart disease (CHD). The Whitehall Study (Fuller et al 1980) demonstrated that significant risk factors for CHD mortality in subjects with IGT include systolic Blood Pressure, resting ECG abnormalities and age; other factors include high density lipoprotein [HDL]-cholesterol, glucose and insulin levels, and BMI - in that study, serum cholesterol did not confer as high a risk of CHD death in the IGT group as in normoglycaemic group.

However, uncertainty still exist concerning the relationship between IGT and Serum Lipoproteins [Capaldo et al 1983, Wilson et al 1981, Ballantyne et al 1977], as varying results have been found in the studies reported. Controversies have arisen because of different diagnostic criteria for IGT used in most studies reported to date (Wilson et al 1981, Ballantyne et al 1977), and because the high prevalence of obesity in IGT may itself have an effect on Serum Lipoproteins (Kannel et al 1979).

A study from the Mayo Clinic reported that hypertriglyceridaemia but not hypercholesterolaemia was associated with IGT independent of body weight (Zimmerman et al 1981). In a study in Italy, it was found that

1) IGT individuals had significantly higher Total Triglyceride levels when compared to normal weight controls but not when compared to BMI matched controls;
2) serum cholesterol levels were similar in the IGT and each of the control groups;
3) there was no significant correlation between serum lipoprotein and blood glucose levels (Capaldo et al 1983).

To date, there have been no reports of epidemiologic studies evaluating serum lipid levels in IGT in South African Indians. In a study of South African Indian myocardial infarct survivors, it was found that abnormal glucose tolerance and lipid abnormalities were significant risk factors in Indian subjects with CAD. (Sewdarsen et al 1983). In that study, when male MI survivors with normal glucose tolerance were compared to those with abnormal glucose tolerance (diabetes mellitus + IGT), it was found that serum triglycerides were higher in those with abnormal glucose tolerance, whilst cholesterol and HDL cholesterol levels were similar in both groups.

This chapter examines the lipid status in the study group at Year 1.

SUBJECTS AND METHODS

SUBJECTS

The study group comprised 128 Indian subjects (67 males and 61 females) who were previously diagnosed as having IGT (as described in chapters 2 and 4).

64 adult Indian subjects (31 males and 33 females) who were matched for age, sex, and BMI served as controls for the study (as described in chapter 2 and 3b).

METHODS

1) A 75G OGTT was performed after an overnight fast, on all the subjects in the study group at Year 1, and on all control subjects (as described in chapter 2 and 4).

In addition, fasting venous blood samples were drawn into plain tubes, for determination of serum total cholesterol (chol), triglyceride (Tg) and high density lipoprotein cholesterol (HDL-chol).

Serum total cholesterol and triglyceride levels were estimated by a semi-automated enzymatic method; and HDL-cholesterol by a precipitation procedure.

2) According to the results of the OGTT at Year 1, the subjects were classified into 3 categories of glucose tolerance (as described in

chapters 2 & 4) viz IGT_1 $Normal_1$ and $Diabetes_1$.

RESULTS

RESULTS ARE SUMMARISED IN TABLE 1 - 11

SERUM TOTAL CHOLESTEROL

TABLE 1 - 6

a) Total study group

Table 1,4

Serum total cholesterol levels were significantly higher in the study group 6.43 ± 0.13 mmol/L compared to the control group 5.98 ± 0.13 mmol/L p = 0.016.

Comparison between the sexes demonstrated that in the study group the mean cholesterol level was similar in both males and females, whilst in the control group it was significantly higher in males 6.25 ± 0.18 mmol/L than in females 5.71 ± 0.19 mmol/L p= 0.04.

For males, mean total cholesterol was similar in the study and control group, whilst for females, the level was significantly higher in the study group 6.38 ± 0.16 mmol/L compared to the control group 5.71 ± 0.18 mmol/L p= 0.0085.

b) According to category of glucose tolerance at Year 1.

Table 2, 3, 5 & 6

TABLE 1

SERUM LIPID PROFILES IN THE STUDY GROUP AND CONTROL GROUP
AT YEAR 1

	TOTAL CHOLESTEROL (mmol/L)	TOTAL TRIGLYCERIDE (mmol/L)	HDL-CHOLESTEROL (mmol/L)
TOTAL SUBJECTS:			
Study Group (n=128)	6.43±0.13(3.9-11.9)	2.19±0.15(0.6-1.5)	1.20±0.07(0.6-9.8)
Control Group(n=64)	5.98±0.13(4.1-9.9)	1.51±0.09(0.63-3.7)	1.18±0.04(0.67-2.1)
P	0.016	0.0001	ns
MALE SUBJECTS:			
Study Group(n=67)	6.49±0.2(3.9-11.9)	2.49±0.24(0.6-10.5)	1.20±0.13(0.7-9.8)
Control Group(n=31)	6.25±0.18(4.1-8.4)	1.77±0.11(0.9-3.6)	1.07±0.06(0.67-2.1)
P	ns	0.007	ns
FEMALE SUBJECTS:			
Study Group(n=61)	6.38±0.16(3.9-9.4)	1.89±0.18(0.7-10.4)	1.21±0.04(0.6-2.1)
Control Group(n=33)	5.71±0.18(4.4-9.9)	1.25±0.11(0.63-3.7)	1.29±0.05(0.8-2.0)
P	0.0085	0.019	ns

Results Expressed As Mean ± SE (Range)

TABLE 4

SERUM LIPID LEVELS AT YEAR 1 : SEX DISTRIBUTION IN STUDY GROUP AND CONTROL GROUP

GROUP	TOTAL CHOLESTEROL MMOL/L	TOTAL TRIGLYCERIDE MMOL/L	HDL-CHOLESTEROL MMOL/L
Study Group (n=128)			
Males (n=67)	6.49±0. 2(3.9-11.9)	2.49±0.24(0.6-10.5)	1.20±0.13(0.7-9.8)
Females (n=61)	6.38±0.16(3.9-9.4)	1.89±0.18(0.7-10.4)	1.21±0.04(0.6-2.1)
P	ns	0.006	ns
Control Group (n=64)			
Males (n=31)	6.25±0.18(4.1-8.4)	1.77±0.11(0.9-3.6)	1.07±0.06(0.8-2.0)
Females (n=33)	5.71±0.19(4.4-9.9)	1.25±0.11(0.6-3.7)	1.29±0.05(0.8-2.0)
P	0.04	0.002	0.009

Results Expressed As Mean ± SE (Range)

When the study group was divided according to the category of glucose tolerance at Year 1, no significant difference was found in Serum Total Cholesterol between the IGT_1 $Normal_1$ and $Diabetes_1$ Groups - this was true when the groups were examined with both sexes combined (Table 2 and 5), as well as when the sexes were examined separately (Table 3).

Comparison between the sexes, for each of the 3 groups studied demonstrated that serum total cholesterol was similar in males compared to females (Table 3).

Intergroup comparison (males and females combined) between the IGT_1 $Normal_1$ $Diabetes_1$ and control group, showed that serum total cholesterol was significantly higher in the IGT_1 group 6.56 ± 0.25 mmol/L compared to control group 5.98 ± 0.13 mmol/L, and between the $Diabetes_1$ group 6.61 ± 0.19 mmol/L compared to the control group 5.98 ± 0.13 mmol/L. (Table 5). However, overall, the difference between the 4 groups fell just short of statistical significance $p = 0.0548$.

For males, intergroup analysis demonstrated no difference in total cholesterol levels between the 4 groups (Table 6); whilst for females, total cholesterol levels were significantly higher in the $Diabetes_1$ group 6.6 ± 0.24 mmol/L compared to the control group 5.71 ± 0.18 mmol/L $p = 0.0045$. For females, total cholesterol levels were higher in the IGT_1 group 6.24 ± 0.27 mmol/L compared to the control group 5.71 ± 0.18 mmol/L, however the difference fell just short of statistical significance ($p = 0.06$).

TABLE 2

SERUM LIPID PROFILES IN STUDY GROUP ACCORDING TO
CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

SERUM LIPID MMOL/L	IGT_1 n=47	$DIABETES_1$ n=41	$NORMAL_1$ n=40	P^+
TOTAL CHOLESTEROL	6.56±0.25(4.1-11.9)	6.61±0.19(4.2-9.1)	6.1 ±0.21(3.9-8.6)	0.27
TOTAL TRIGLYCERIDE	$1.9 \pm 0.12 (0.7-4.7)^B$	$2.78 \pm 0.33 (0.8-10.4)^A$	$1.96 \pm 0.31 (0.6-10.5)^B$	0.006
HDL-CHOL	1.30±0.19(0.7-9.8)	1.12±0.04(0.6-2.0)	1.17±0.05(0.6-2.1)	0.591

Results Expressed As Mean ± SE (Range)
$^+$ P values for the comparisons between the three groups by anaylsis of variance
A,B: Mean values with the same letter are not significantly different

TABLE 3

SERUM LIPID LEVELS AT YEAR 1 : SEX DISTRIBUTION IN THE STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE

GLUCOSE TOLERANCE GROUP (n)	TOTAL CHOLESTEROL MMOL/L	TOTAL TRIGLYCERIDE MMOL/L	HDL-CHOLESTEROL MMOL/L
IGT_1 (47)			
Males (28)	6.78±0.37(4.1-11.9)	2.05±0.17(1.0-4.9)	1.39±0. 3(0.7 -9.8)
Females (19)	6.24±0.27(4.6- 9.4)	1.67±0.14(0.7-3.3)	1.17±0.07(0.73-2.0)
P	0.29	0.12	0.57
$Diabetes_1$ (41)			
Males (15)	6.65±0.31(5.1-9.1)	3.5 ±0. 6(1.1- 9.8)	1.01±0.03(0.8-1.2)
Females (26)	6.60±0.24(4.2-8.5)	2.35±0.38(0.8-10.4)	1.19±0.06(0.6-2.0)
P	0.90	0.095	0.016
$Normal_1$ (40)			
Males (24)	6.05±0.27(3.9-8.6)	2.36±0. 5(0.6-10.5)	1.08±0.05(0.8-1. 8)
Females (16)	6.18±0.35(3.9-8.5)	1.38±0.15(0.8-2.5)	1.30±0.09(0.6-2.17)
P	0.73	0.19	0.023

Results Expressed As Mean ± SE (Range)

TABLE 5

SERUM LIPIDS IN THE STUDY GROUP BASED ON THE CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1, AND IN THE CONTROL GROUP: INTERGROUP COMPARISON

MEAN SERUM LIPID MMOL/L	IGT_1	$DIABETES_1$	$NORMAL_1$	CONTROL	P^+
TOTAL CHOL	6.56^A	6.61^A	6.1^{AB}	5.98^B	0.055
TOTAL Tg	1.9^B	2.78^A	1.96^B	1.51^B	0.001
HDL-CHOL	1.30^A	1.12^A	1.17^A	1.18^A	0.68

$^+$ P values are for the comparison between the four groups by analysis of variance
A,B: Mean values with the same letter are not significantly different

TABLE 6

SERUM LIPIDS IN THE STUDY GROUP BASED ON THE CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1, AND IN THE CONTROL GROUP: INTERGROUP COMPARISONS

MEAN SERUM LIPID (MMOL/L)	MALES				FEMALES			
	IGT_1	$DIABETES_1$	$NORMAL_1$	CONTROL	IGT_1	$DIABETES_1$	$NORMAL_1$	CONTROL
TOTAL CHOL	6.78	6.65	6.05	6.25	6.24	6.60°	6.18	5.71
TOTAL Tg	2.05^{*}	3.5^{++}	2.36^{+}	1.77	1.67°	2.35°	1.38^{+}	1.25
HDL-CHOL	1.39	1.01	1.08	1.07	1.17	1.19	1.30	1.29

$^{++}$ $P<0.05$; $^{\circ}$ $P<0.01$ indicate significant difference between group and control subjects
* $P<0.05$; indicates significant difference between IGT_1 and $Diabetes_1$ groups
$^{+}$ $P<0.05$; indicates significant difference between $Normal_1$ and $Diabetes_1$ groups

SERUM TOTAL TRIGLYCERIDE

Table 1 - 6

a) Total Study Group

Table 1, 4

The serum total triglyceride was significantly higher in the study group 2.19 ± 0.15 mmol/L compared to the control group 1.51 ± 0.09 mmol/L, $p = 0.0001$.

In both the study and control groups, total triglyceride levels were significantly higher in males compared to females. In the study group, the mean total triglyceride level in males (2.49 ± 0.24 mmol/L) was higher than in females (1.89 ± 0.18 mmol/L), $p = 0.002$.

When the sexes were examined separately, serum total triglyceride level was significantly higher in the study group compared to the control group, for both males and females. For males, the mean total triglyceride was 2.49 ± 0.24 mmol/L in the study group compared to the control group, 1.77 ± 0.11 mmol/L $p = 0.007$; in females, levels in the study group (mean 1.89 ± 0.18 mmol/L) was higher compared to the control group (mean 1.25 ± 0.11 mmol/L), $p = 0.019$.

b) according to category of glucose tolerance at Year 1

Table 2,3,5 & 6

When the study group was divided according to the category of glucose tolerance at Year 1, total triglyceride levels were significantly higher in the $Diabetes_1$ group 2.78 ± 0.33 mmol/L compared to both the IGT_1 group 1.9 ± 0.12 mmol/L and the $Normal_1$ group 1.96 ± 0.31 mmol/L (Table 5 & 2).

Comparison between the sexes demonstrated that total triglyceride levels were similar in males and females, for each of the 3 study groups studied (Table 3).

For both males and females, the levels were highest in the $Diabetes_1$ group. For males total triglyceride was significantly higher in the $Diabetes_1$ group 3.5 ± 0.6 mmol/L compared to the IGT_1 group 2.05 ± 0.17 mmol/L p = 0.017. For females, intergroup comparison revealed no significant difference in serum triglyceride levels (Table 6).

Intergroup comparisons (males and females combined) between the IGT_1 $Normal_1$ $Diabetes_1$ and Control group (Table 5) demonstrated that serum total triglyceride was significantly higher in the $Diabetes_1$ group when compared to Control, IGT_1 and $Normal_1$ groups. There was no significant difference in total triglyceride levels between the IGT_1 group and Control group.

For males, intergroup comparison revealed higher total triglyceride levels in $Diabetes_1$ group 3.5 ± 0.6 mmol/L compared to the Control group 1.77 ± 0.11 mmol/L p = 0.014; IGT_1 males had higher levels than Control males, 2.05 ± 0.12 mmol/L vs 1.77 ± 0.11 mmol/L; the difference however was not significant (Table 6).

For females intergroup analysis demonstrated that total triglyceride was significantly higher in the IGT_1 group 1.67 ± 0.14 mmol/L when compared to the control group 1.35 ± 0.11 mmol/L p = 0.0028, and in the $Diabetes_1$ group 2.35 ± 0.38 mmol/L compared to the control group 1.25 ± 0.11 mmol/L p = 0.009 (Table 6).

SERUM HDL - CHOLESTEROL

Table 1 - 6

a) Total Study Group

Table 1 & 4

No significant difference was found in HDL Cholesterol between the study group and the control group - this was true when the groups were examined with both sexes combined, as well as when males and females were examined separately. Serum HDL cholesterol in the study group was 1.20 ± 0.07 mmol/L and in the control group, 1.18 ± 0.04 mmol/L.

Comparison between the sexes demonstrated that in the study group, HDL cholesterol levels were similar in males 1.20 ± 0.13 mmol/L compared to females 1.21 ± 0.04 mmol/L; whilst in the control group, males had significantly lower levels 1.07 ± 0.06 mmol/L compared to females 1.29 ± 0.06 mmol/L p = 0.009.

b) according to category of glucose tolerance at Year 1

Table 2, 3, 5, & 6

When the study group was divided according to the category of glucose tolerance at Year 1, serum HDL cholesterol was higher in the IGT_1 group 1.30 ± 0.19 mmol/L compared to the $Diabetes_1$ group 1.12 ± 0.04 mmol/L and $Normal_1$ groups 1.117 ± 0.05 mmol/L; however, there was no significant difference between the 3 groups, both when the sexes were combined (Table 2 & 5) as well as when males and females were examined separately (Table 3).

Comparison between the sexes, for each of the 3 groups studied, demonstrated that HDL cholesterol was significantly lower in males than females in $Diabetes_1$ and $Normal_1$ groups; for the IGT_1 group, levels were similar in males and females (Table 3).

Intergroup comparison between the IGT_1 $Diabetes_1$ $Normal_1$ and control groups, demonstrated no significant difference in HDL cholesterol levels between the 4 groups, whether the sexes were examined combined or separately (Table 5 & 6).

PREVALENCE OF SERUM LIPID ABNORMALITIES AT YEAR 1

Table 7 - 11

(a) Hypercholesterolaemia

Table 7 - 9

The prevalence of hypercholesterolaemia was high in both the study and control group. When the Total Study Group was examined, 42.9%, 59.4% and 78.9% had Serum Cholesterol ≥6.5, ≥6.1, ≥5.2 mmol/L, respectively. Of the Control Group, 30%, 46.9% and 73.3% had Serum Cholesterol ≥6.5, ≥6.1, ≥5.2 mmol/L respectively.

When the study group was divided according to the category of glucose tolerance, over 40% of the IGT_1, $Diabetes_1$ and $Normal_1$ groups has serum cholesterol ≥6.5mmol/L; with a cut-off level of ≥5.2mmol/L, hypercholesterolaemia was observed in 67.5%, 78.7% and 90.2% of the $Normal_1$, IGT_1 and $Diabetes_1$ groups respectively.

(b) Hypertriglyceridaemia

Table 7,8,10

Of the Total Study Group, 37.5% and 50.8% had Serum Triglyceride ≥2.0 and ≥1.7mmol/L, respectively. Of the Control group, 23.3% and 28.3% had Serum Triglyceride ≥2.0 and ≥1.7mmol/L, respectively.

Based on the category of glucose tolerance of the study group, Serum Triglyceride ≥2.0mmol/L was found in 25%, 31.9% and 56.1% of the $Normal_1$, IGT_1 and $Diabetes_1$ groups, respectively; with a cut-off level of ≥1.7mmol/L, the prevalence was 32.5%, 51.1% and 68.3% respectively.

(c) ↓Serum HDL-Cholesterol

Table 7,8,11

11.7% and 15% of the Total Study group and Control group, respectively, had Serum HDL-Cholesterol <0.9mmol/L.

Based on the category of glucose tolerance of the Study group, ↓ serum HDL-Cholesterol was observed in 7.5%, 14.9% and 12.2% of the $Normal_1$, IGT_1 and $Diabetes_1$ groups, respectively.

TABLE 7

PREVALENCE OF SERUM LIPID ABNORMALITIES AT YEAR 1:
BASED ON CATEGORY OF GLUCOSE TOLERANCE

GROUP (number examined)		*HYPERCHOLESTEROLAEMIA %	*HYPERTRIGLYCERIDAEMIA %	*↓HDL-CHOLESTEROL %
IGT_1	(47)	78.7	51.1	14.9
$DIABETES_1$	(41)	90.2	68.3	12.2
$NORMAL_1$	(49)	67.5	32.5	7.5
TOTAL STUDY GROUP	(128)	78.9	50.8	11.7
CONTROL GROUP	(64)	73.3	28.3	15.0

*Serum Cholesterol ≥ 5.2 mmol/L
Serum Triglyceride ≥ 1.7 mmol/L
Serum HDL-Cholesterol < 0.9 mmol/L

TABLE 8

PREVALENCE OF SERUM LIPID ABNORMALITIES AT YEAR 1:
BASED ON CATEGORY OF GLUCOSE TOLERANCE

GROUP (number examined)		*HYPERCHOLESTEROLAEMIA %	*HYPERTRIGLYCERIDEMIA %	*↓HDL-CHOLESTEROL %
IGT_1	(47)	40.4	31.9	14.9
$DIABETES_1$	(41)	46.3	56.1	12.2
$NORMAL_1$	(40)	42.5	25.0	7.5
TOTAL STUDY GROUP	(128)	42.9	37.5	11.72
CONTROL GROUP	(64)	30.0	23.3	15.0

*Serum Cholesterol ≥ 6.5 mmol/L
Serum Triglyceride ≥ 2.0 mmol/L
Serum HDL-Cholesterol < 0.9 mmol/L

Table 9

PREVALENCE OF HYPERCHOLESTEROLAEMIA AT YEAR 1:
BASED ON CATEGORY OF GLUCOSE TOLERANCE

GROUP (number examined)		PREVALENCE (%) FOR SERUM CHOLESTEROL (mmol/L)			
		≥6.5	≥6.1	≥5.7	≥5.2
IGT_1					
Male	(28)	42.9	64.3	75.0	78.6
Female	(19)	36.8	47.4	68.4	78.9
Total	(47)	40.4	57.5	72.3	78.7
$DIABETES_1$					
Male	(15)	46.7	73.3	73.3	93.3
Female	(26)	46.2	69.2	76.9	88.5
Total	(41)	46.3	70.7	75.6	90.2
$NORMAL_1$					
Male	(24)	41.7	50.0	58.8	66.7
Female	(16)	43.8	50.0	50.0	68.8
Total	(40)	42.5	50.0	55.0	67.5
TOTAL STUDY GROUP					
Male	(61)	43.3	61.2	68.7	77.6
Female	(67)	42.6	57.4	67.2	80.3
Total	(128)	42.9	59.4	67.9	78.9
CONTROL GROUP					
Male	(31)	40.0	32.8	70.0	80.0
Female	(33)	20.0	14.9	46.7	66.7
Total	(64)	30.0	46.9	58.3	73.3

Table 10

PREVALENCE OF HYPERTRIGLYCERIDAEMIA AT YEAR 1:
BASED ON CATEGORY OF GLUCOSE TOLERANCE

GROUP (number examined)		PREVALENCE (%) FOR SERUM TRIGLYCERIDE (mmol/L) ≥2.0	≥1.7
IGT_1			
Male	(28)	42.9	60.7
Female	(19)	15.8	36.8
Total	(47)	31.9	51.1
$DIABETES_1$			
Male	(15)	80.0	80.0
Female	(26)	42.3	61.5
Total	(41)	56.1	68.3
$NORMAL_1$			
Male	(24)	29.2	37.5
Female	(16)	18.8	25.0
Total	(40)	25.0	32.5
TOTAL STUDY GROUP			
Male	(67)	46.3	56.7
Female	(61)	27.9	44.3
Total	(128)	37.5	50.8
CONTROL GROUP			
Male	(31)	36.7	43.3
Female	(33)	10.0	13.3
Total	(64)	23.3	28.3

Table 11

PREVALENCE OF ↓ SERUM HDL-CHOLESTEROL:
BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

GROUP	(number examined)	SERUM HDL-CHOLESTEROL < 0.9 mmol/L %
IGT_1		
Male	(28)	17.9
Female	(19)	10.5
Total	(47)	14.9
$DIABETES_1$		
Male	(16)	13.3
Female	(25)	11.5
Total	(41)	12.2
$NORMAL_1$		
Male	(24)	8.3
Female	(16)	6.3
Total	(40)	7.5
TOTAL STUDY GROUP		
Male	(67)	13.4
Female	(61)	9.8
Total	(128)	11.7
CONTROL GROUP		
Male	(31)	26.7
Female	(33)	3.3
Total	(64)	15.0

DISCUSSION

While prospective studies have highlighted an increased risk of macrovascular disease, especially CHD, with IGT, any definite relationship between IGT and serum lipids and lipoprotein abnormalities has not been established.

Several epidemiologic studies on IGT have demonstrated an increased frequency of morbidity and mortality from macrovascular disease, especially CHD (Fuller et al 1980, Jarrett et al 1976, Jarrett et al 1982). However, the mechanism for predisposition to the development of atherosclerotic complications in IGT subjects remains unclear. The Whitehall study (Fuller et al 1980) demonstrated that significant predictive risk factors for CHD mortality in subjects with IGT include systolic blood pressure, resting ECG abnormalities and age; other factors included HDL cholesterol, glucose and insulin levels and BMI; in that study, serum cholesterol did not confer as high a risk of CHD death in the IGT group as in the normoglycaemic group.

Serum lipid and lipoprotein abnormalities are well known risk factors for the development of atherosclerosis (Carlson et al 1972, Brown et al 1965, Santen et al 1972, Goldstein et al 1973, Kannel et al 1979, Barboriak et al 1979, Miller et al 1979). It has been well demonstrated that CHD in established NIDDM is associated with abnormalities of serum lipid and lipoprotein metabolism (Jarrett et al 1982, Ohlson et al 1986, Tzagournis and Falko 1982). However, as regards the relationship between IGT and serum lipoprotein abnormalities, conflicting results have been shown in the studies published. (Capaldo et al 1983, Wilson et al 1981, Ballantyne et al 1977, Zimmerman et al 1981, Falko et al 1987, Puavilai et al 1988) and it is unclear whether the increased risk for CHD in IGT, is due at all, to abnormal lipid and lipoprotein metabolism.

Controversies surrounding IGT and lipid aberrations exist because a wide range of diagnostic criteria for IGT were employed in the earlier studies (Wilson et al 1981, Ballantyne et al 1977). Moreover, factors viz. age, sex and obesity are known to influence serum lipid even concentration (Lewis et al 1974). In recent years even studies using more uniform diagnostic criteria for IGT have failed to resolve the question. Therefore the overrall impression is that no major lipid/lipoprotein abnormality is associated with IGT (Zimmerman et al 1981, Falko et al 1987, Capaldo et al 1983, Ganda et al 1985, Puavilai et al 1988).

In a study from the Mayo Clinic (Zimmerman et al 1981) it was found that apart from slight elevations of total and VLDL triglyceride (independent of body weight), IGT subjects showed similar lipid levels to those of control subjects, and it was suggested that perhaps some of the IGT subjects may actually have had the impaired glucose tolerance of familial hypertriglyceridaemia rather than diabetes. However, in the present study, control subjects were age, sex and BMI matched; therefore any alteration in lipids would probably reflect the influence of glucose tolerance. In that study, compared to the diabetic group, subjects with IGT had higher HDL cholesterol levels and lower total triglyceride levels, but total cholesterol levels were similar.

In an Italian study (Capaldo et al 1983), IGT subjects were found to have significantly higher total triglyceride levels compared to normal weight controls, but not when compared to age, sex and body weight matched controls; total cholesterol levels were similar in the IGT and each of the control groups. The finding in that study suggested that in individuals with IGT, no major lipid or lipoprotein abnormality exists, which is independent of obesity, and that other factors viz hypertension, obesity and platelet abnormalities often associated with IGT may contribute to the higher risk for atherosclerosis in such subjects. In Calpaldo's study IGT males showed significantly higher triglyceride, when compared to normal weight controls; whilst serum total cholesterol and HDL cholesterol levels were similar in the IGT and control groups. For females, total triglyceride levels were significantly higher than both weight matched and normal weight control subjects.

A study on 215 volunteers, which was undertaken at a Metabolic Clinic in the U.K. (Falko et al 1987), assessed the relationship between serum lipoproteins and varying degrees of glucose tolerance. In that study, both for males and females, there was no significant difference in serum total cholesterol, total triglyceride or HDL cholesterol levels between IGT and control subjects. LDL cholesterol was found to be significantly higher in IGT males compared to male controls. Other intergroup analyses in that study demonstrated that for females, total cholesterol was significantly higher in the Diabetic group compared to the IGT group; HDL cholesterol which was lowest in the Diabetes group, was significantly lower compared to the control group only but not to the IGT group. For males, total triglyceride was significantly higher and HDL cholesterol significantly lower in the Diabetic group compared to the IGT and control group. Like the present study, diabetic patients were newly diagnosed untreated diabetics.

Of relevance in that study was the finding that when compared to the control group, no dramatic alterations in lipid levels existed in subjects with IGT.

In a recent study comparing serum lipid levels in 150 Thai subjects with IGT to those in 138 age, sex and BMI matched control subjects, the only significant difference was found with total cholesterol levels in females, those with IGT having higher levels (Puavilai et al 1988).

In a study on off-springs of two Type II diabetic patients (Ganda et al 1985), significant alterations of plasma lipids were found in female subjects with IGT, but not in males. Total cholesterol and triglyceride levels were significantly higher and HDL cholesterol significantly lower in IGT females compared to female controls. Of note in that study, is that firstly, the study group was a biased group, being off-springs of two diabetic parents; secondly, that the study conditions differed - 100G oral glucose load was used for the OGTT; and thirdly, only seven of the 41 subjects with abnormal glucose tolerance could be classified as IGT by NDDG criteria.

In the present study, when the study group was examined as a whole (ie. IGT_1, $Diabetes_1$ and $Normal_1$ Groups), serum total cholesterol and total triglyceride were significantly higher when compared to the control group, but no difference was found in HDL cholesterol between the two groups. For total triglyceride, this was true for both males and females; however, serum cholesterol was only significantly higher than control group in females and not in males. The finding of higher serum cholesterol levels in females accords with the results of Puavilai (1988), Capaldo (1983) and Ganda (1985). However, caution should be exercised when assessing Capaldo's study, which only showed a difference when the study group was compared to normal weight controls, and not when compared to body weight matched controls, as was the case in the present study.

The finding in the present study of higher serum total triglyceride in both males and females, is at variance with the studies quoted above: Ganda (1985) found that total triglyceride was significantly higher only in females, whilst Capaldo showed that in females, total triglyceride was higher in IGT compared to both weight matched and normal weight controls, and in males the levels were only significantly higher when compared to normal weight control subjects. Falko (1987) and Puavilai (1988) found no difference in total triglyceride levels in IGT compared to control subjects.

That no difference was found in HDL cholesterol, is in keeping with most other quoted reports (Capaldo et al 1983, Puavilai et al 1988, Falko 1987, Zimmerman et al 1981) except for Ganda (1985) who found lower HDL cholesterol in IGT females.

The above comparisons between the present and quoted studies are those for the study group as a whole, but of note, is that whilst all the study subjects were IGT a year previously, at the time that serum lipids were examined, these subjects had already entered into their first year (Year 1) of the natural history of their IGT and hence were either IGT_1, $Normal_1$ $Diabetes_1$ (newly diagnosed diabetes).

When the study group was divided according to the category of glucose tolerance at Year 1, (males and females combined) serum cholesterol was significantly higher in the IGT_1 group compared to the control group. This is at variance with the findings of Zimmerman (1981) and Capaldo (1983) who found no difference in total cholesterol levels. Comparison with the studies of Falko, Puavilai and Ganda is not possible since these studies did not examine serum lipid levels with the sexes combined. Serum total triglyceride was similar in the IGT_1 and control groups. Both Zimmerman (1981) and Capaldo (1983) demonstrated significantly higher total triglyceride levels in IGT compared to control groups, although in Capaldo's study, this was true only when IGT subjects were compared to normal weight controls. The finding that there was no difference in HDL cholesterol levels in the IGT_1 group and Control groups, confirms the findings of Zimmerman (1981) and Capaldo (1983). Additional intergroup analysis in the present study demonstrated that serum total cholesterol was similar and total triglyceride significantly lower in the IGT_1 group compared to the $Diabetes_1$ group, a finding similar to that of Zimmerman (1981).

For males, intergroup analysis demonstrated no difference in serum total cholesterol, triglyceride and HDL cholesterol in IGT_1 group and control groups, confirming the findings of Ganda (1985), Falko (1987), Puavilai (1988) and Capaldo (1983); of note, is that Capaldo (1983) found higher total triglyceride in IGT males only when compared to normal weight controls.

For females, intergroup analysis revealed significantly higher total triglyceride in the IGT_1 group compared to the control subjects, confirming the results of Capaldo (1983) and Ganda (1985), but at variance with that of Falko and Puavilai who found no difference. Although total cholesterol was higher in IGT_1 females than control subjects, the difference fell just short of statistical significance. While Falko found no difference, Ganda and Puavilai found higher total cholesterol in IGT females; in Capaldo's study this difference was only noted when comparison was made with normal weight controls. That HDL cholesterol levels were similar in IGT_1 females and controls, endorses the results of Falko, Puavilai and Capaldo; only Ganda found lower levels in IGT females.

Thus the findings in the present study were that the IGT_1 group had significantly higher serum total cholesterol than control subjects, (contributed to by the difference in females), and that total triglyceride was significantly higher only in IGT_1 females.

In conclusion, the present study has shown and confirmed earlier reports that no major alterations in lipid metabolism exist with IGT and that if present, are more prevalent in females than males.

SUMMARY

Serum lipid levels were evaluated at Year 1, in 128 study subjects (67 males and 61 females) who were previously diagnosed as having IGT, and in 64 control subjects (31 males and 33 females). Study subjects were further divided according to the category of glucose tolerance at Year 1 viz. IGT_1 $Normal_1$, $Diabetes_1$.

When the study group was examined as a whole, serum total cholesterol was significantly higher 6.43 ± 0.13 mmol/L compared to the control group, 5.98 ± 0.13 mmol/L $p = 0.016$: In females, levels were significantly higher in the study group, whilst in males, there was no difference between the study group and control group. Serum total triglyceride was significantly higher in the study group 2.19 ± 0.15 mmol/L, compared to the control group 1.51 ± 0.09 mmol/L $p=0.001$; for both males and females the levels were significantly higher in the study group. No difference was found in HDL cholesterol, between the study and control groups.

When the study group (males and females combined) was divided according to the category of glucose tolerance, and compared to the control group, serum total cholesterol was significantly higher in the IGT_1 group 6.25 ± 0.25 mmol/L compared to the control group 5.98 ± 0.13 mmol/L. No significant difference was found in total triglyceride and HDL cholesterol levels between IGT_1 and control groups. For females, serum total cholesterol was higher in the IGT_1 group 6.24 ± 0.27 mmol/L, compared to female controls 5.71 ± 0.18 mmol/L; however the difference fell just short of statistical

significance p = 0.06. IGT_1 females had significantly higher total triglyceride 1.67 ± 0.14 mmol/L than female controls 1.25 ± 0.11 mmol/L p = 0.029. HDL cholesterol was similar in the two groups.

For males, whilst serum triglyceride was higher in the IGT_1 group than the male controls, the difference was not significant. No difference was found in total and HDL cholesterol between the two groups.

Further intergroup analyses revealed total triglyceride levels were significantly higher in the $Diabetes_1$ group compared to the other three groups. (sexes combined). For females, total cholesterol and triglyceride was highest in the $Diabetes_1$ group and significantly higher than only the control group. $Diabetes_1$ males had the highest total triglyceride level, which was significantly higher when compared to the other three groups.

Analyses of sex distribution for each of the categories studied, demonstrated that in the control group, serum total cholesterol and triglyceride were significantly higher and HDL cholesterol significantly lower in males than in females. In the IGT_1 group no difference was observed in total and HDL cholesterol and total triglyceride, between males and females. In both the $Diabetes_1$ and $Normal_1$ group, serum total cholesterol and triglyceride were similar in males and females, whilst HDL cholesterol was significantly lower in males than females.

CHAPTER 9

GLYCOSYLATED HAEMOGLOBIN (GHb) IN THE STUDY GROUP AT YEAR 1

INTRODUCTION

The Oral glucose tolerance test (OGTT) is the gold standard for the diagnosis of diabetes mellitus and other categories of glucose tolerance. The Introduction of the revised diagnostic criteria and classification by National Diabetes Data Group (1979) and WHO (1980, 1985) was met with widespread acceptance, since they introduced uniformity and standardisation in the diagnosis of diabetes mellitus and other categories of glucose tolerance.

Measurement of glycosylated haemoglobin (GHb) has been suggested as an alternative to OGTT for diabetes screening and diagnosis (Dods and Bolmey 1979, Simon et al 1985, Santiago et al 1978). The rationale for its use is that whereas performance of an OGTT is time consuming, expensive and physically demanding on the individual being tested (WHO 1980), GHb can be performed in a non-fasted state requiring only one blood sample (Gabbay et al 1979)and facilitating compliance. Moreover the results of the OGTT vary with age, activity level, metabolic stress, time of day and other factors (O'Sullivan and Mahan 1968, Sherwin RS 1977, Campbell et al 1975, Committee of Statistics of the ADA 1969); whilst measurement of GHb is not influenced by recent activity levels, metabolic stress and food intake (Gabbay et al 1979).

Whilst measurement of GHb is now widely used for monitoring long term glucose control in known diabetic patients, its potential value as a technique for screening and diagnosis of diabetes has not been thoroughly established (Little et al 1988).

Glycosylated haemoglobin (GHb) is a minor component of adult haemoglobin (the major component being Hb Ao). GHb is formed by a post-translational non-enzymatic glycosylation of haemoglobin by an aldehyde-containing molecule such as glucose, depending on the degree and duration of hyperglycaemia (Klenk et al 1982). This glycosylation may either be a stable, irreversible linkage, or a labile, reversible linkage.

In the labile form of linkage, glucose is believed to be able to form reversible Schiff base adducts with the N-terminus of both a and B chains of the haemoglobin, as well as with certain E -amino groups of lysine residues on both a and B chains. The labile fraction increases with acute changes of blood glucose i.e. they reflect short term fluctuations of blood glucose.

When the glycosylation is a stable, irreversible linkage, a stable Ketamine complex is formed, which is commonly referred to as "glycosylated haemoglobin" (GHb). GHb concentration is increased in erythrocytes of diabetic patients and serves as an indirect measure of integrated plasma glucose level over the previous 2 - 3 months. When the stable glycosylation occurs at the N-terminus of the β-chain, it is referred to as HbA_1 which is the most abundant form of stable GHb.

HbA_1 itself exists in 3 forms viz: HbA_{1c} (which is the major constituent of HbA_1), HbA_{1a} and HbA_{1b} - therefore HbA_1 = $HbA_{1[a+b+c]}$. However HbA_1 is not the only form of stable GHb; i.e Stable GHb consists of a heterogeneous population of haemoglobin variants, which were not routinely measured until the advent of affinity chromatography (Bunn et al 1979, Klenk et al 1982). Total GHb refers to stable + labile fractions.

Several studies have examined the relationship between GHb and OGTT (Little et al 1988). However, comparisons between the various studies have several drawbacks because of differences in criteria used for the diagnosis of diabetes during an OGTT, differences in fractions of GHb which were measured, as well as variations in methods employed for measuring the same fraction.

Techniques for measuring GHb include chromatography (ion-exchange or affinity), electrophoresis, colorimetry, fluorimetry, radioimmuno assay and iso-electric focusing (Klenk et al 1982). These techniques measure different fractions of the GHb. The most commonly employed method for the quantitation of GHb is cation-exchange chromatography. One of the problems encountered with measurement of HbA_1 by ion-exchange chromatography, (and the earlier measurements for HbA_{1c}) was the interference by "labile" fractions, giving falsely elevated results; however it has been shown that the difference between the GHb level that included the reversible component and the level consisting of the stable moiety alone, was relatively small, with the maximal fluctuation being not more than 1.5% over 2 - 12 hours (Bolli et al

1980, Botterman 1981). Moreover, the maximal changes only occured in the range from 14%—15%, whereas at lower levels the differences were very small and only slightly above the range of error of methodology (Botterman 1981). Thus it was concluded that in the clinical context, greater fluctuations of GHb values in the range of 14% to 15% are of little significance because patients with such high values are already in poor control.

This chapter describes the relationship between glycosylated haemoglobin and OGTT in the study subjects at Year 1.

SUBJECTS AND METHODS

SUBJECTS:

The study group comprised 128 Indian subjects (67 males and 61 females) who were previously diagnosed as having IGT (as described in Chapter 2 - 4).

64 adult Indian subjects (31 males and 33 females) who were matched for age, sex and BMI, served as controls for the study (as described in Chapter 2 and 3b).

METHODS:

1) At Year 1, a 75 - G OGTT was performed after an overnight fast on all study subjects and control subjects (as described in Chapter 2). Plasma glucose was determined using a glucose oxidase method.

2) In addition, fasting venous blood samples were collected into EDTA-containing blood tubes for the determination of Haemoglobin A_1 (HbA_1), a glycosylated haemoglobin.

HbA_1 ($HbA_{1[a+b+c]}$) was measured using the Helena GLYCO Hb QUICK COLUMN PROCEDURE, which is a cation-exchange microchromatographic method for the quantitation of HbA_1.

The normal range for HbA_1 at the local laboratory is 3.46% - 8,42% (Mean ± SD 5.94 ± 1.24), determined with the same assay, for a South African Indian population. The range was calculated as Mean ± 2SD.

3) According to the results of the OGTT at Year 1, the study subjects were further classified into 3 categories of glucose tolerance viz IGT_1 $Diabetes_1$ $Normal_1$ (as described in Chapter 2 and 4).

STATISTICAL ANALYSIS

Statistical analyses were performed with programs of the SAS institute. Comparisons amongst the 4 groups (or 3 groups) were performed by analsysis of variance (ANOVA) GLM [general linear model] program). Duncan's multiple range test was employed to evaluate the difference between any two groups studied.

Statistical correlations were obtained by Pearson's r coefficient and the regression lines calculated by the least squares method. The comparison of the slopes of the regression lines was obtained by student's t test for differences between regression slopes.

Since 3 of the control subjects had spuriously high levels of GHb, they were excluded from the statistical analysis.

RESULTS

Results are shown in Table 1 - 4, Figure 1,2

A. Study Group As A Whole

The Mean HbA_1 in the study group (7.43 ± 1.48%) was higher than that in the control group (6.99 ± 1.22%), but the difference was not significant, Table 1 and Figure 2. There was a significant correlation between GHb and both fasting and 2-hr plasma glucose

Table 1

GLYCOSYLATED HAEMOGLOBIN (HbA1) IN THE STUDY GROUP

AND CONTROL GROUP AT YEAR 1

	STUDY GROUP	CONTROL GROUP	P
NUMBER	128	64	
SEX (MALE:FEMALE)	67:61	31:33	
+PLASMA GLUCOSE (mmol/L)			
0 min	6.49±0.14(3.4-11.6)	5.42±0.11(3.4-7.7)	0.0001
120 min	10.01±0.36(2.4-23.7)	5.22±0.15(2.7-7.5)	0.0001
*HbA_1 (%)	7.34±1.48(2.6-13.1)	6.99±1.22(3.6-8.9)	ns

+Mean ± SE (Range)

*Mean ± SD (Range)

($r=0.31, p<0.0001$; $r=0.19$, $p<0.0001$, respectively).

B Study Group Based on Category of Glucose Tolerance at Year 1.

Table 2-4 Figure 1,2

As shown in Table 2, the overall interaction between the 3 study groups, using analysis of variance (ANOVA), fell short of statistical significance ($p=0.06$). However, using Duncan's multiple range test, the Mean GHb level was significantly higher in the Diabetes_1 group 7.61 ± 1.76%, compared to the Normal_1 group 6.90 ±1.12%. The Mean GHb in the IGT_1 group was 7.48 ± 1.44%; however, there was no significant difference in Mean GHb between the IGT_1 group and the other 2 study groups.

Figure 1 demonstrates the distribution of individual GHb values for the 3 groups. 8 of the 47 subjects (17%) from the IGT_1 group and 11 of the 41 subjects (26.8%) from the Diabetes_1 group had high GHb values (above the upper limit for normal i.e. 8.42%). 1 subject (2.5%) from the Normal_1 group exhibited high levels. 1 subject (2.4%) from the Diabetes_1 group had GHb value which was below the lower limit of normal levels (Figure 1, Table 4).

Figure 2 demonstrates the relationship between GHb levels and fasting 2-hr plasma glucose levels for the three study groups. For the IGT_1 and Normal_1 groups, there was no significant correlation between GHb and both fasting and 2-hr plasma glucose. For the subjects in the

Table 2

GLYCOSYLATED HAEMOGLOBIN (HbA1) IN THE STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE AT YEAR 1

	CATEGORY OF GLUCOSE TOLERANCE			+P
	IGT_1	$DIABETES_1$	$NORMAL_1$	
NUMBER	47	41	40	
++PLASMA GLUCOSE				
0 min	6.3 ±0.12(4.5-7.7)^{A}	7.88±0.25(5.5-11.6)^{B}	5.32±0.15(3.4-7.7)^{C}	0.0001
120 min	9.37±0.15(7.8-11.0)^{A}	14.69±0.52(11.1-23.7)^{B}	5.95±0.2(2.4-7.6)^{C}	0.0001
*HbA (%)	7.48±1.44(4.9-13.1)^{AB}	7.61±1.76(2.6-11.4)^{A}	6.90±1.12(3.4-9.3)^{B}	0.06

++mmol/L Mean ± SE (Range)

*Mean ± SD (Range)

+P values are for comparisons between the 3 groups by analysis of variance

Mean values with the same letter are not significantly different

$Diabetes_1$ group, there was significant correlation between GHb and fasting plasma glucose (r=0.55, p0.0002); 9 of the 18 diabetic subjects who had FBG ≥ 7.8 mmol/ℓ had high GHb levels, whilst only 2 of 23 diabetic subjects with FBG < 7.8mmol/ℓ, had a high value.

C Study Group vs Control Group: based on category of glucose tolerance at Year 1.

Table 3,4 Figure 1,2

The Mean GHb was highest in the $Diabetes_1$ group, lowest in the $Normal_1$ group, with intermediate values in the remaining two groups (i.e. $Diabetes_1$ → IGT_1 → Control → $Normal_1$). Comparison between the 4 groups by ANOVA, demonstrated significant overall interactions for Mean GHb (p=0.04). Using Duncan's multiple range test, Mean GHb was significantly higher in the $Diabetes_1$ group 7.61 ± 1.76%, compared to the Control group 6.99 ± 1.22% and the $Normal_1$ group 6.9 ± 1.12% respectively. There was no significant difference in the Mean GHb level between the IGT_1 group, and each of the other 3 groups.

Figure 1 demonstrates the individual GHb values for each of the 4 groups. The majority of the individuals, irrespective of category of glucose tolerance, had GHb levels well within the normal range. As described above, only 17% and 26.8% of the IGT_1 and $Diabetes_1$ groups, respectively, had high GHb levels. 9 of the 64 control subjects (14%) exhibited high GHb values. There was marked overlap between the 4 groups. The specificity for GHb as a measure of normal glucose

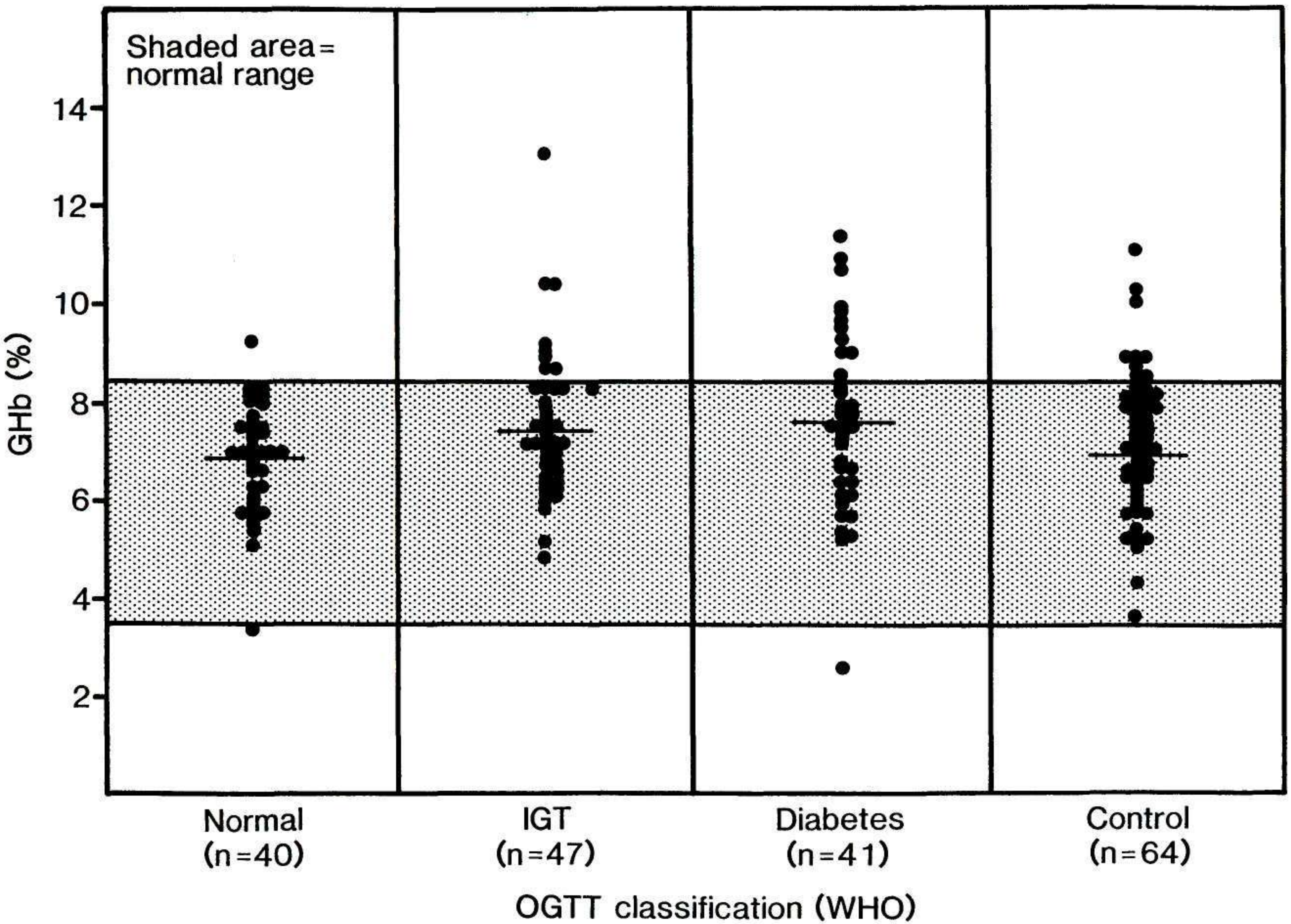


Figure 1: GHb (HbA_1) levels at Year 1:basedon category of glucose tolerance.

Table 3

GLYCOSYLATED HAEMOGLOBIN (HbA1) BASED ON THE CATEGORY

OF GLUCOSE TOLERANCE AT YEAR 1: STUDY GROUP AND CONTROL GROUP

	CATEGORY OF GLUCOSE TOLERANCE				
	IGT_1	$DIABETES_1$	$NORMAL_1$	CONTROL	^+P
NUMBER	47	41	40	64	
$^{++}$PLASMA GLUCOSE					
0 min	6.30^B	7.88^A	5.32^C	5.42^C	0.0001
120 min	9.37^B	14.69^A	5.95^C	5.22^C	0.0001
$^*HbA_1$ (%)	$7.48^{A,B}$	7.61^A	6.90^B	6.99^B	0.04

$^{++}$mmol/L Mean values

* Mean values

+P values are for comparisons between the 4 groups by analysis of variance

Mean values with the same letter are not siginificantly different.

tolerance was 85.9%, Fig 2, Table 4.

Figure 2 demonstrates the relationship between GHb and both fasting and 2-hr plasma glucose values for the 4 groups. For the IGT_1, $Normal_1$ and Control groups, there was no significant correlation found between GHb and both fasting and 2-hr plasma glucose; whilst in $Diabetes_1$ group, there was a significant correlation between GHb and fasting plasma glucose ($r=0.55$, $p<0.0002$).

Table 4

DISTRIBUTION OF GLYCOSYLATED HAEMOGLOBIN (HbA1) AT YEAR 1

BASED ON CATEGORY OF GLUCOSE TOLERANCE

	CATEGORY OF GLUCOSE TOLERANCE			
	IGT_1	$DIABETES_1$	$NORMAL_1$	CONTROL
+HbA_1 (%)	7.48±1.44	7.61±1.76	6.90±1.12	6.99±1.22
*Abnormal HbA_1 (n)	8	11	1	9
*Normal HbA_1 (n)	39	30	39	55
Total subjects (n)	47	41	40	64

Sensitivity for IGT	8 of 47 (17%)
Sensitivity for D	11 of 41 (26.8%)
Sensitivity for IGT and D	19 of 88 (21.6%)
Specificity	55 of 64 (85.9%)

+Mean ± SD

*Abnormal HbA1 > 8.42% (Mean ± 2SD)

Normal HbA1 ≤ 8.42% (Mean ± 2SD)

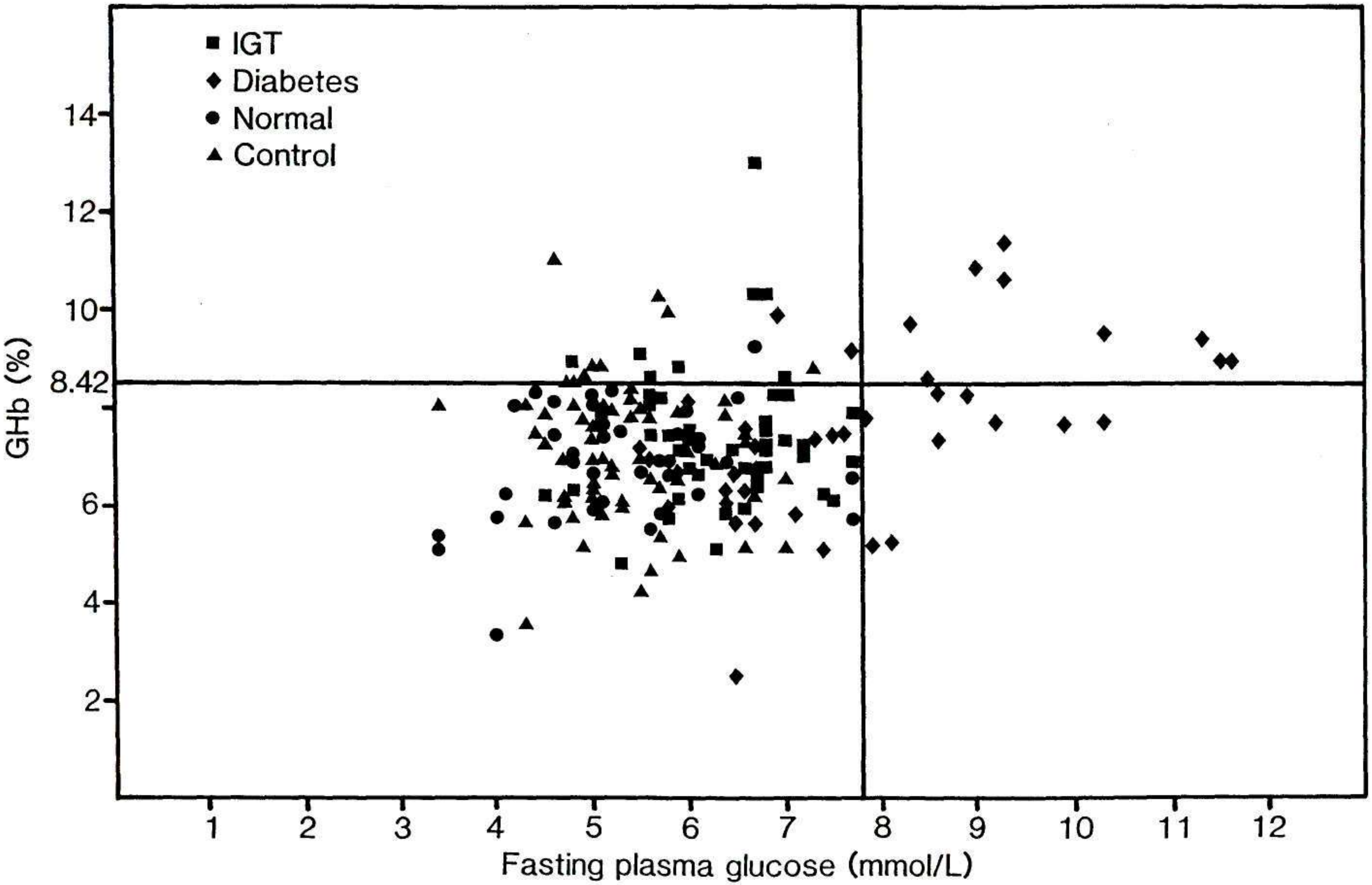


Figure 2: Scattergrams of GHb (HbA$_1$) vs fasting plasma glucose: based on category of glucose tolerance at Year 1.

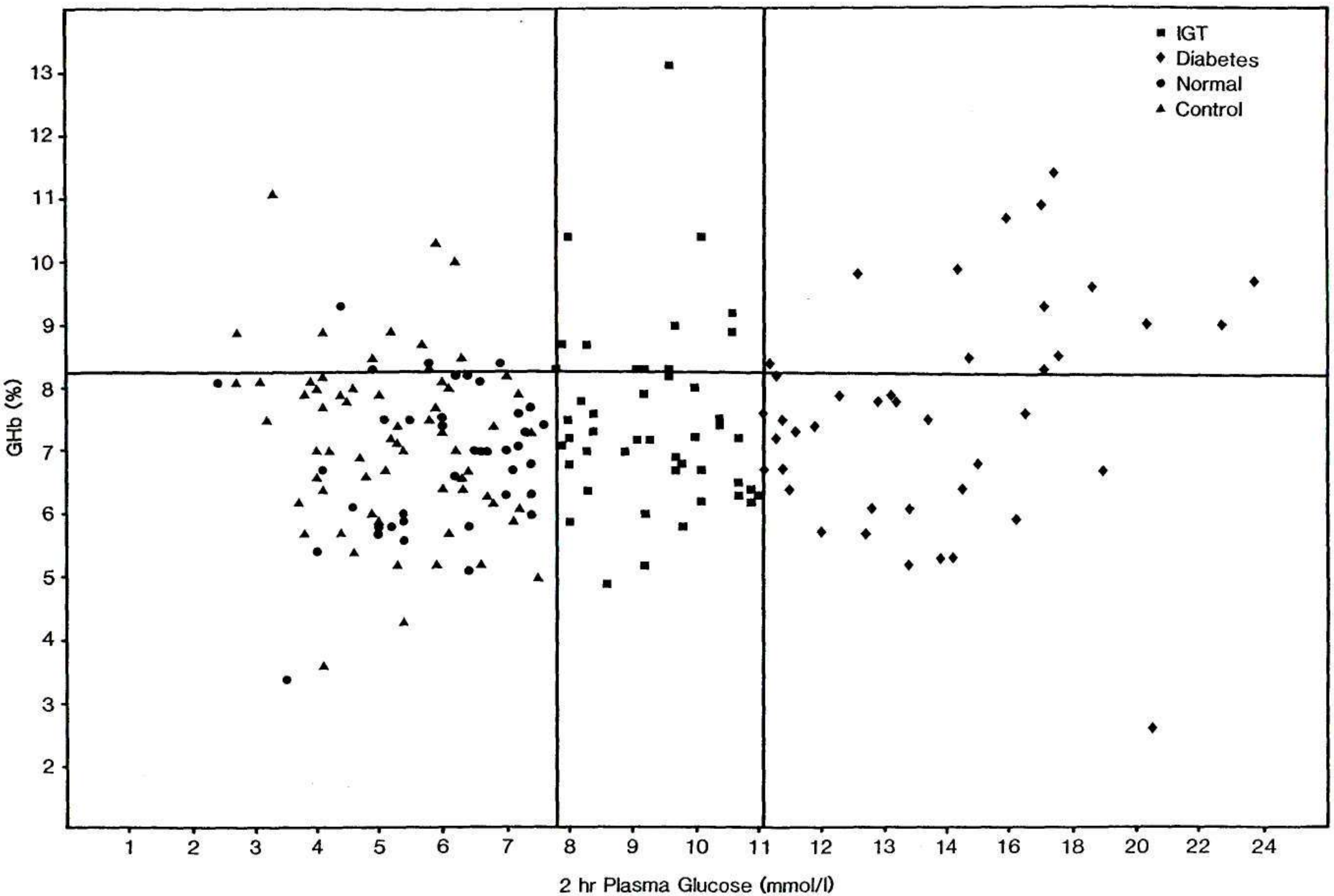


Figure 3: Scattergrams of GHb (HbA$_1$) vs 2 hr. plasma glucose: based on category of glucose tolerance at Year 1.

Table 5 **Correlation Analysis**

Group (n)	HbA_1 plasma glucose 0min	HbA_1 plasma glucose 120min
Study + Control (192)	0.31 ($p<0.001$)	0.2 ($p<0.01$)
Control (64)	0.01 (p-)	-0.21 (p-)
Normal (40)	0.23 (p-)	0.2 (p-)
IGT (47)	0.05 (p-)	-0.06 (p-)
Diabetes (41)	0.55 ($p<0.001$)	0.28 (p-)

Results: correlation coefficient r (p value)
p- not significant

DISCUSSION

The potential value of glycosylated haemoglobin (GHb) measurement as a technique for screening and diagnosis of glucose tolerance has not been thoroughly established, despite several studies which have examined the relationship between GHb and OGTT with a view to investigating the feasability of using GHb as an indicator in the diagnosis and detection of diabetes mellitus (Little et al 1988), Santiago et al 1978, Kesson et al 1982, Simon et al 1985, Dods and Bolmey 1979, Flock et al 1979, Bolli et al 1980, Manicardi et al 1981, Orchard et al 1982, Modan et al 1984, Ferrel et al 1984, Hall et al 1984, Lester et al 1985).

However, comparisons between these studies are hampered by the following:

1) Different criteria employed in the earlier studies for the diagnosis of diabetes.
2) Different fractions of GHb measured.
3) Different techniques employed by measuring the same fraction of GHb.
4) Different normal ranges for GHb, making international standardisation impossible.

The different fractions/populations of GHb measured include:

1) HbA_{1c} (Little et al 1988, Kesson et al 1982, Simon et al 1985 , Svendson et al 1980, Santiago et al 1978, Koenig et al 1976,

Trivelli et al 1971).

2) HbA_1 ($HbA_{1[a+b+c]}$) (Kesson et al 1982, Modan et al 1988, Lester et al 1985, Modan et al 1984, Ferrel et al 1984, Verrillo et al 1983, Manicardi et al 1981, Bolli et al 1980, Fiock et al 1979, Dods and Bolmey 1979).

3) Total glycosylated haemoglobin (Stable+Labile) - (Klenk et al 1982, Hall et al 1983, 1984).

4) Stable glycosylated haemoglobin (Total - Labile) - (Klenk et al 1982, Hall et al 1983, 1984).

In the present study HbA_1 ($HbA_{1[a+b+c]}$) was measured by cation - exchange microchromatographic method.

Many techniques have been employed for measuring GHb viz. chromatography (ion-exchange or affinity), electrophoresis, calorimetry, fluorimetry, radioimmunoassay and iso-electric fosusing (Klenk et al 1982). These methods can be considered in two categories; there are those that separate parts of the GHb by means of their very small charge differences (viz ion-exchange and electrophoretic methods) and there are those that make use of the CHO portion of the GHb (viz. calorimetry and affinity chromatography).

Chromatography, especially ion-exchange chromatography, has been the technique employed in most of the studies quoted above; these include measurement of HbA_{1c} by high - performance liquid chromatography (HPLC) (Little et al 1988, Svendson et al 1980, Santiago et al 1979); measurement of HbA_{1c} by the method of Trivelli (Koenig et al 1976, Kesson et al 1982, Simon et al 1985). Ion-exchange chromatography has also been the basis for the widely available mini-columns employed to measure $HbA_{1[a+b+c]}$ (Modan et al 1984, Kesson et al 1982, Ferrel et al 1984, Verrillo et al 1983, Manicardi et al 1981, Dods and Bolmey 1979), and measurement of $HbA_{1[a+b+c]}$ by modified methods (Flock et al 1979, Bolli et al 1980). Affinity chromatography is a method used for measuring Total and Stable GHb (Klenk et al 1982, Hall et al 1983, 1984).

Unlike measurement of HbA_{1C} (by HPLC) which measures the irreversibility glycosylated fraction only, estimation of HbA_1 by ion-exchange chromatography includes the "labile" fraction (the reversible fraction reflecting short term fluctuations in blood glucose) which might affect results by giving falsely elevated HbA_1 levels (Little et al 1988). Moreover, the mini-columns employing ion-exchange chromatography are highly sensitive to ph, temperature, ion-concentration and presence of abnormal haemoglobins. However these methodological problems are common to most methods employing ion-exchange chromatography and not confined to mini-column methods only (Jovanovic and Peterson 1981, Klenk et al 1982).

It has been reported that compared to $OGTT_1$, HbA_{1c} measurement is not sufficiently sensitive in the screening of diabetes, both when this was the only measure of GHb (Santiago et al 1978, Koenig et al 1978), as well as when HbA_{1c} was compared to HbA_1 (Kesson et al 1982). On the other hand measurement of HbA_1 appeared to be more sensitive in the screening of diabetes even when it was the only measure of GHb employed (Dods and Bolmey 1979). Notwithstanding, the methodological problems associated with ion-exchange chromatography (Jovanovic and Peterson 1981) were found in all these studies.

Affinity chromatography for measuring GHb (Total or Stable) is reported to be unaffected by moderate fluctuations of ph, temperature or presence of abnormal haemoglobins; hence the measure of Stable GHb by affinity chromatography would appear to obviate both problems associated with ion-exchange chromatography viz the methodogical problems of interference by ph, temperature and ion concentration common to all ion-exchange methods, as well as the possible interference by "labile" fractions with HbA_1 measurement by ion-exchange methods. However, reported studies using affinity chromatography for Stable GHb are few (Hall et al 1983, 1984).

Notwithstanding the aforementioned problems there have been several important studies which have examined the relationship between GHb and OGTT. In general, studies have shown that GHb correlates with various parameters of OGTT (Little et al 1988).

As regards the value of GHb in the detection of IGT, most studies have demonstrated considerable overlap in GHb between IGT and normal glucose tolerance groups, and have concluded that GHb is relatively insensitive for detection of IGT. (Little et al 1988, Santiago et al 1978, Flock et al 1979, Manicardi et al 1981, Modan et al 1984, Verrillo et al 1983). A few studies however, have shown that Mean GHb was significantly higher in the IGT compared to Normal groups (Little et al 1988, Verrillo et al 1983, Hall et al 1984).

A study examining the relationship between HbA_{1c} and OGTT, and the value of GHb in diabetes screening was undertaken in 381 Pima Indians who were participants of a longitudinal epidemiologic study of diabetes. The subjects in that study were divided into 3 OGTT classes based on WHO criteria (N, IGT and Diabetes). Mean HbA_{1c} was significantly higher in the IGT compared to the Normal groups. However, GHb was insensitive in identifying IGT (only 30% of IGT subjects had high HbAlc), moderately sensitive (85%) in identifying Diabetes, but highly specific in excluding abnormal glucose tolerance (91% of Normal group had normal GHb). Whilst a high HbA_{1c} usually indicated IGT or Diabetes, a normal level did not exclude such a diagnosis. Of interest in that study was that those IGT subjects with high GHb levels had significantly higher fasting plasma glucose values than those with normal GHb. The author made the point that the central purpose of most screening programs is to identify subjects with diabetes at an early stage, so that they might have the advantage of early treatment to prevent complications of the disease; Yet the results of that study confirmed that GHb was relatively insensitive for detecting subjects with IGT and that normal GHb did not exclude a diagnosis of diabetes - it was therefore concluded that unless it can be determined whether GHb would be as good as a single fasting or 2-hr post load plasma glucose, in predicting complications of diabetes (i.e. longitudinalstudies), GHb cannot be substituted for OGTT in the screening of diabetes (Little et al 1988).

In another study of 300 Pima Indians with varying degrees of glucose tolerance, it was found that Mean HbA_1 did not differ significantly between the IGT and N groups (although HbA_1 in the Diabetes group was significantly higher). The conclusion in that study was that measurement of GHb failed to discriminate between those with mild impairment of glucose tolerance and those with normal glucose tolerance and that GHb provided no great advantage over fasting and/or 2-hr plasma glucose for the diagnosis of diabetes (Flock et al 1979).

Overlap in GHb levels between IGT and Normal subjects, has been confirmed by other workers, irrespective of whether HbA_{1c} (Santiago et al 1978) or HbA_1 levels (Modan et al 1984, Verrillo et al 1983, Manicardi et al 1981) have been measured.

Some studies have shown significant difference in Mean GHb levels between IGT and N groups (Little et al 1988, Verrillo et al 1983, Hall et al 1984). Of note, though, is that the first two quoted also demonstrated considerable overlap in Ghb distribution between IGT and normal subjects. In the third study (Hall et al 1984), total and stable GHb levels were measured by affinity chromatography in 53 subjects (31 N, 17 D and 5 IGT): it was found that there was a significant difference in stable (and Total) GHb between the 3 groups; that all the subjects with IGT and Diabetes had GHb values above normal; that there was overlap between IGT and Diabetic group but not between IGT and Normal group; and that none of the N subjects had high GHb values. However, a major limitation of this study, is that only 5 subjects with IGT were studied.

The results in the present study indicate that Mean HbA_1 in the IGT_1 group does not differ significantly from that of the Control group, and that GHb is relatively insensitive for diagnosis of IGT, with considerable overlap in GHb levels between the IGT and Control groups; GHb was found to be moderately specific (85.9% of the Control group had normal GHb levels) for excluding abnormal glucose tolerance.

Therefore, the findings in the present study, viz: insensitivity of GHb in diagnosis of IGT, are compatible with all the above quoted studies except one (Hall et al 1984); however, as stated above, the small sample size of IGT subjects in that study hampers comparison.

The observation in the present study that Mean GHb in the IGT_1 group did not differ significantly from that of the Control group, whilst compatible with most other resports, is at variance with a few (Little et al 1988, Verrillo et al 1983, Hall et al 1984). However, as explained earlier, the first two studies also demonstrated overlap and insensitivity of GHb, whilst the third study was limited by sample size. From literature review, it would appear that when the value of GHb is being investigated in the diagnosis of diabetes; it is the distribution of GHb, rather than the Mean levels of GHb in different groups of glucose tolerance, which yields more valuable information.

In the present study the finding of considerable overlap in GHb values between the IGT_1 and $Diabetes_1$ group, is compatible with that of other workers (Little et al 1988, Verrillo et al 1983, Hall et al 1984). Again, at variance with those studies, was that there was no significant difference in Mean GHb between the IGT_1 and $Diabetes_1$ group. These findings may be attributed to the fact that in the present study the diabetic subjects were newly diagnosed diabetics.

As regards GHb and the diagnosis/detection of diabetes, the observation in the present study that the $Diabetes_1$ group had significantly higher Mean GHb compared to the Control group, is in agreement with other reported studies (Little et al 1988, Flock et al 1979, Hall et al 1984, Verrillo et al 1983, Santiago et al 1978, Kesson et al 1982, Ferrel et al 1980). However, the insensitivity of GHb in detection of diabetes found in the present study (26.8%), as well as the overlap, is at variance with all except two of the afore mentioned studies: Santiago et al (1978) found high HbA_1 levels in only 53% of diabetic subjects; Kesson et al (1982) found that using HbA_1, 91% of diabetics had high levels, but when HbA_{1c} was measured, only 43% had elevated levels. The findings in the present study may be explicable on the basis that the $Diabetes_1$ group comprised newly diagnosed diabetic subjects.

A significant correlation between GHb and both fasting and 2-hr plasma glucose was demonstrated in the present study; this is compatible with other reported studies (Little et al 1988, Hall et al 1984, Verrillo et al 1983, Flock et al 1979, Santiago et al 1978).

The observation in the present study that 3 subjects in the Control group had spuriously high GHb values was somewhat surprising. However in a study of 648 individuals with normal glucose tolerance 12.1% were found to have significantly high HbA_1 levels (Modan et al 1988). In that study, no correlation was found with other correlates of glucose tolerance, caloric intake or physical activity. Moreover, in the 3.5 year follow up of these subjects, the rate of deterioration of glucose tolerance was similar to that of a Control group. It was concluded that factors unrelated to glucose tolerance may be the main determinants of GHb levels in subjects with normal glucose tolerance, or that GHb levels display biologically significant between-individual variability, unrelated to glycaemia.

In conclusion, the present study has demonstrated that GHb (HbA_1) is relatively insensitive in the detection of both IGT and Diabetes, with considerable overlap between these groups and the Control group, and that GHb is a poor substitute for OGTT in the diagnosis of IGT and diabetes.

SUMMARY

Glycosylated haemoglobin [specifically HbA_1 ($HbA_{1[a+b+c]}$)] and its relationship with OGTT was studied at Year 1 in 128 Study subjects (61 males and 67 females) who were previously diagnosed as having IGT, and in 64 Control subjects (31 males and 33 females). The Study subjects were further classified according to the category of glucose tolerance at Year 1, based on WHO criteria (IGT_1 $Normal_1$ $Diabetes_1$).

The Mean GHb in the Study group (7.34±1.48%), did not differ significantly from that of the Control group 6.99±1.22%. There was a significant correlation between GHb and both fasting and 2-hr plasma glucose ($r=0.31$, $p<0.0001$; $r=0.19$, $p<0.0001$, respectively).

When the study group was divided according to the category of glucose tolerance at Year 1, and compared to the Control group, the Mean GHb was significantly higher in the $Diabetes_1$ group 7.61±1.76% compared to the Control group 6.99±1.22% and the $Normal_1$ group 6.9±1.12%, respectively. There was no significant difference for Mean GHb between the IGT_1 group 7.48±1.44% and each of the other three groups.

Compared to the OGTT, GHb was relatively insensitive in the diagnosis of IGT or Diabetes: only 17% and 26.8% of the IGT_1 and $Diabetes_1$ groups respectively, had elevated GHb. The majority of individuals, irrespective of the category of glucose tolerance, had GHb within the normal range.

For the IGT_1 $Normal_1$ and Control groups, no significant correlation was found between GHb and both fasting and 2-hr plasma glucose. For the $Diabetes_1$ group, there was significant correlation between GHb and fasting plasma glucose ($r=0.55$, $p<0.0002$).

CHAPTER 10

PLASMA URIC ACID AND GLUCOSE TOLERANCE AT YEAR 1

INTRODUCTION

Uric acid is the end product of purine metabolism. Plasma uric acid levels are genetically determined, though influenced by multiple environmental factors. Several studies have been undertaken to evaluate the distribution of plasma uric acid in different ethnic groups, and to establish whether there is an association between plasma uric acid and diseases such as clinical gout, diabetes mellitus, coronary heart disease and hypertension (Tuomilehto et al 1988).

A negative association between plasma uric acid and overt diabetes has been demonstrated in earlier studies, which employed different diagnostic criteria for diabetes (Mikkelson et al 1965, Zalokar et al 1972, Klein et al 1973, Herman et al 1967, Hasslacker et al 1974, Myers et al 1968, Beckett AG and Lewis JG 1960, Herman et al 1976, Herman JB and Goldbourt U 1982).

In a prospective study of 10,000 Israeli men, serum acid levels were found to be significantly higher in "pre-diabetic" men compared to diabetic and non-diabetic men (Herman et al 1976).

The first study to examine plasma uric acid and glucose tolerance, using WHO criteria was undertaken in a biracial population of Fiji. In that study, plasma uric acid levels were highest in subjects with Impaired glucose tolerance and lowest in diabetic subjects, especially in diabetic men; the strongest predictor of plasma uric acid was found to be plasma creatinine (Tuomilehto et al 1988).

In the present study, plasma uric acid determination was primarily undertaken for investigation of cardiovascular risk factors in IGT subjects. It was the finding of the Fijian study (Tuomilehto et al 1988) that prompted a study of the relationship between plasma uric acid and glucose tolerance. This chapter examines plasma uric acid in the study group at Year 1.

PATIENT AND METHODS

SUBJECTS:

The study group included 128 Indian subjects (67 males and 61 females) who were previously diagnosed IGT, based on WHO criteria (as described in Chapter 2 - 4).

64 Indian subjects (31 males and 33 females) who were matched for age, sex and Body Mass Index (BMI) served as controls for the study (as described in Chapter 2 and 3b).

METHODS:

1) At Year 1, a 75G oral glucose tolerance test (OGTT) was performed after an overnight fast, on all subjects (as described in Chapter 2).

2) In addition, venous blood samples were drawn into plain tubes, for measurements of plasma uric acid concentration. Plasma uric acid was determined by an enzymatic colorimetric method.

Hyperuricaemia was defined as plasma uric acid levels $\geq$ 0.42 mmol/L in males, and $\geq$ 0.36 mmol/L in females.

RESULTS

Results are summarised in Table 1 - 7

1) Plasma Uric Acid Concentration

Table 1 - 4

No significant difference was observed in Mean plasma uric acid level between the study group and control group; this was true whether the study group was examined as a whole (Total study group) or when divided according to category of glucose tolerance (IGT_1 $Diabetes_1$ $Normal_1$) and whether the sexes were examined separately or combined.

When the sexes were compared, the mean plasm uric was significantly higher in males compared to females, in the $Normal_1$ group ($p < 0.05$) and control group ($p < 0.05$).

Table 1

PLASMA URIC ACID (mmol/L) AT YEAR 1:

STUDY GROUP AND CONTROL GROUP

	STUDY GROUP	CONTROL	P
NUMBER	128	64	
SEX (male:female)	67:61	31:33	
+ BMI	25.8±0.4(16.8-40.7)	24.3±0.6(14.7-35.6)	
+ PLASMA GLUCOSE (mmol/L)			
0 min	6.5±0.1(3.4-11.6)	5.4±0.1(3.4-7.7)	0.0001
120 min	10.0±0.4(2.4-23.7)	5.2±0.2(2.7-7.5)	0.0001
+ PLASMA URIC ACID (mmol/L)	0.36±0.01(0.12-1.4)	0.34±0.02(0.17-1.28)	ns
+ Mean ± SE (Range)			

Table 2

PLASMA URIC ACID (mmol/L) AT YEAR 1:

STUDY GROUP AND CONTROL GROUP

	*PLASMA URIC ACID (mmol/L)
TOTAL SUBJECTS:	
Study Group (n=128)	0.36±0.01 (0.12-1.41)
Control Group (n=64)	0.34±0.02 (0.17-1.28)
P	ns
MALE SUBJECTS:	
Study Group (n=67)	0.39±0.02 (0.22-1.41)
Control Group (n=31)	0.38±0.03 (0.17-1.28)
P	ns
FEMALE SUBJECTS:	
Study Group (n=61)	0.33±0.01 (0.12-0.67)
Control Group (n=33)	0.29±0.03 (0.17-1.08)
P	ns
*** Mean ± SE (Range)**	

Table 3

PLASMA URIC ACID (mmol/L) AT YEAR 1 : STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE

	IGT_1	$DIABETES_1$	$NORMAL_1$	CONTROL	P
NUMBER	47	41	40	64	
* URIC ACID (mmol/L)	0.36±0.02(0.2-0.93)	0.35±0.01(0.21-0.67)	0.36±0.03(0.12-1.41)	0.34±0.02(0.17-1.28)	ns

* Mean ± SE (Range)

Table 4

PLASMA URIC ACID AT YEAR 1 : SEX DISTRIBUTION IN STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE

GROUP	*PLASMA URIC ACID (mmol/L)				++P
	n	MALES	n	FEMALES	
IGT_1	28	0.38±0.03(0.26-0.93)	19	0.33±0.02(0.2-0.47)	ns
$DIABETES_1$	15	0.36±0.02(0.22-0.51)	26	0.35±0.02(0.210.67)	ns
$NORMAL_1$	24	0.41±0.05(0.27-1.41)	16	0.29±0.02(0.12-0.40)	0.047
CONTROL	31	0.38±0.03(0.17-1.28)	33	0.29±0.03(0.17-1.08)	0.047
+P		ns		ns	

* Mean ± SE (Range)

\+ P values are for comparison between the four groups by an analysis of variance

++P values are for comparison between sexes in each group

2) Prevalence of Hyperuricaemia

Table 5 -7

a) Total study group:

Hyperuricaemia was found in 25.8% of the study group and 15.3% of the control group; however the difference was not significant.

In females, the prevalence of hyperuricaemia was significantly higher in the study group (32.8%) compared to the control group (13.3%) $p=0.048$.

b) Study group based on category of glucose tolerance:

Hyperuricaemia was found in 36.6%, 25.5%, 15% and 15.3% of the $Diabetes_1$ IGT_1 $Normal_1$ and control groups, respectively; there was a significant overall difference between the groups ($p=0.046$).

For females, the prevalence of hyperuricaemia was significantly higher in $Diabetes_1$ and IGT_1 groups (46.2% and 31.6%, respectively) compared to the control group (13.3%) $p=0.02$

c) All subjects (study and control group)

When all subjects were examined, hyperuricaemia was observed in 21.9%, the prevalence in females being 25.5%, and in males 18.4%.

Table 5

PREVALENCE OF *HYPERURICAEMIA AT YEAR 1

	HYPERURICAEMIA %
TOTAL SUBJECTS	
Study Group (n=128)	25.8
Control Group (n=64)	15.3
P	ns
MALE SUBJECTS:	
Study Group (n=67)	19.4
Control Group (n=31)	17.2
P	ns
FEMALE SUBJECTS:	
Study Group (n=61)	32.8
Control Group (n=33)	13.3
P	0.048

* Plasma uric acid ≥ 0.42 in males
≥ 0.36 in females

Table 6

PREVALENCE OF *HYPERURICAEMIA AT YEAR 1 : STUDY GROUP BASED ON CATEGORY OF GLUCOSE TOLERANCE

SEX	CATEGORY OF GLUCOSE TOLERANCE				P
	IGT_1 %	$DIABETES_1$ %	$NORMAL_1$ %	CONTROL %	
COMBINED	25.5	36.6	15.0	15.3	0.046
MALE	21.4	20.0	16.7	17.2	ns
FEMALE	31.6	46.2	12.5	13.3	0.02

* Plasma uric acid ≥ 0.42 in males
≥ 0.36 in females

Table 7

PREVALENCE OF HYPERURICAEMIA (all Subjects) AT YEAR 1

	NUMBER EXAMINED	*HYPERURICAEMIA %
TOTAL (male+female)	192	21.9
MALES	98	18.4
FEMALES	94	25.5

* Plasma uric acid ≥ 0.42 in males
≥ 0.036 in females

DISCUSSION

The introduction of the category of Impaired Glucose Tolerance (IGT) by the NDDG (1979) and WHO (1980, 1985) has been a relatively recent one. Whilst there have been reports (albeit a few) on the significance of this category with respect to subsequent development of diabetes and its association with macrovascular disease, the only report regarding the association between plasma uric acid and IGT using WHO criteria, is that of a study undertaken in a biracial population in Fiji (Tuomilehto et al 1988).

A negative association of plasma uric acid with diabetes mellitus has been demonstrated in earlier studies which used varying criteria for glucose tolerance (Mikkelson et al 1965, Zolokar et al 1972, Klein et al 1973, Herman et al 1967, Hasslacker et al 1974, Myers et al 1968, Beckett AG and Lewis JG 1960, Herman et al 1976, Herman JB and Goldbourt U 1982), and confirmed using WHO criteria (Tuomilehto et al 1988).

Prior to the introduction of WHO criteria, in a prospective study of 10,000 Israeli men, it was found that "pre-diabetic" men had higher plasma uric acid levels than men with diabetes and normal glucose tolerance. In that study it was questioned whether the hyperuricaemic tendency was part of a "constellation" of abnormalities found in the "pre-diabetic" state viz obesity / hypertension / hyper -cholesterolaemia/hyperuricaemia syndrome (emphasising the close metabolic ties between those conditions, hyperuricaemia and the subsequent development of diabetes itself (Herman et al 1976).

In a study based on WHO criteria for glucose tolerance, Plasma uric acid and its association with the disease was examined in Melanesians and Asian Indians in Fiji, as part of a population survey on diabetes and cardiovascular risk factors (Tuomilehto et al 1988). It was found that (a) plasma uric acid levels were elevated in subjects with IGT whilst the lowest levels were found in diabetic subjects; (b) BMI was found to have a significant impact on uric acid levels both in non-diabetic and diabetic subjects; (c) the strongest predictor of plasma uric acid was found to be the plasma creatinine, suggesting a strong renal involvement in the balance of plasma uric acid and reflection of dietary patterns; (d) the prevalence of hyperuricaemia was high in both Melanesians and Asian Indians.

Of note though, is that whilst plasma uric acid levels were elevated in both males and females with IGT, the finding of the lowest levels in diabetic subjects was true only for males; diabetic females did not have significantly lower mean plasma uric acid than non-diabetic females.

Although obesity was positively associated with plasma uric acid, it did not explain the high levels in subjects with IGT: in the Normal and Diabetes group, obese males and females had higher Mean plasma uric acid than non-obese subjects; however in males with IGT, there was no significant difference in Mean plasma uric acid between obese and non-obese subjects - therefore the differences between the three groups (IGT, Normal, Diabetes) were not due to differences in BMI alone.

The present study demonstrated that there was no significant difference in Mean plasma uric acid between the study group and control group; this was true whether the study group was examined as a whole (Total study group) or based on the category of glucose tolerance (IGT_1 $Diabetes_1$ $Normal_1$) and whether the sexes were examined separately or combined.

Therefore the finding in the present study are at variance with those quoted above which found increased plasma uric acid levels in IGT subjects. However, as stated above, little information exists in the literature regarding the relationship between plasma uric acid and IGT using WHO criteria, and only confirms the need for further population studies.

The negative association between plasma uric acid and diabetes found in the studies quoted above was not confirmed in the present study in which the levels were similar in the $Diabetes_1$ and control groups. It could be argued that these were newly diagnosed diabetic subjects; nowithstanding, in the Israeli study (Herman et al 1976) even newly diagnosed diabetic men were found to have lower levels than non-diabetic subjects, and in the Fijian study (Tuomilehto et al 1988) the Mean plasma uric acid level was similar in previously and newly diagnosed male diabetic subjects.

It is not clear whether in the present study, the lack of a significant difference in uric acid levels between the $Diabetes_1$ group and Control group could be explained by the higher proportion of females in the $Diabetes_1$ group; since in the Fijian study, whilst mean plasma uric acid was lowest in the Diabetes group when the sexes were examined combined, for females the levels were similar in the diabetic and non-diabetic subjects (Tuomilehto et al 1988).

Obesity has been found to be positively associated with plasma uric acid (Tuomilehto et al 1988); perhaps it could be argued that in the present study the lack of a significant difference in uric acid levels between the categories of glucose tolerance (IGT_1 $Diabetes_1$ $Normal_1$ and control group) could be explained because the control subjects were BMI matched to the study subjects; however, in the Fijian study, the IGT group had highest plasma uric acid levels, despite the fact that for males, the mean values were similar in obese and non-obese subjects - therefore the differences between the categories of glucose tolerance were not due to differences in BMI alone; and obesity alone could not explain the high plasma uric acid levels in subjects with IGT.

An unexpected finding in the present study was the high prevalence of hyperuricaemia in the IGT_1 group (25.5%) and $Diabetes_1$ group (36.6%) compared to the $Normal_1$ (15%) and control group (15.3%), contributed to by the higher prevalence in females, for each of the groups. Thus, whilst the mean plasma uric acid was similar in the various categories of glucose tolerance, there appears to be a definite relationship between hyperuricaemia and glucose tolerance, especially since the $Normal_1$ group (which was IGT a year previously) had a lower prevalence of hyperuricaemia at Year 1. The significance of this finding is not established, and as stated earlier, the primary reason for plasma uric acid determination in the present study was for investigation of cardiovascular risk factors in IGT subjects and no information on clinical gout was obtained. Clearly, what is required is further investigation of the relationship between plasma uric acid and glucose tolerance, possibly through analysis of plasma uric levels in the study subjects at Year 2 and Year 4.

Moreover, comparison with the Fijian study (Tuomilehto et al 1988) is not possible; in that study the overall prevalence of hyperuricaemia was examined and found to be high; however the prevalence of hyperuricaemia in the different categories of glucose tolerance was not examined. In the present study, when all subjects were combined (study and control group) the prevalence of hyperuricaemia in males (18.4%) was similar to that found in Asian Indian males (22%) in the Fijian study; however the prevalence in females (25.5%) in the present study was more than twice that found in Fijian Asian Indian females (11%).

In the present study, plasma uric acid was examined as one of the risk factors for coronary heart disease (as described in Chapter 7) - plasma uric acid was found to be significantly associated with IHD (as indicated by "Abnormal" ECG) particularly for females (Total study group, IGT_1 $Diabetes_1$); the prevalence of hyperuricaemia was found to be higher in subjects with "Abnormal" ECG compared to those with "Normal" ECG (Total study group, control group, IGT_1, $Diabetes_1$).

Whether the relationship between glucose tolerance and plasma uric acid/hyperuricaemia is a causal one, or on the basis that both share a common risk for coronary heart disease, is at present unclear.

Therefore in conclusion, the present study has demonstrated no significant difference in Mean plasma uric acid between the various categories of glucose tolerance at Year 1 (IGT_1 $Diabetes_1$ $Normal_1$ Control); however, the prevalence of hyperuricaemia was found to be high, particularly in the IGT_1 group and Diabetes group, contributed to by the high prevalence in females in each of these groups.

SUMMARY

At Year 1, plasma uric acid was investigated in 128 study subjects (67 males and 61 females) who were diagnosed IGT a year previously, and in 64 control subjects (31 males and 33 females). The study group was further divided according to the category of glucose tolerance at Year 1 viz IGT_1 $Diabetes_1$ $Normal_1$.

No significance difference was observed in Mean plasma uric acid between the study group and control group; this was true when the study group was examined as a whole (Total study group) as well as when the study group was divided according to the category of glucose tolerance (IGT_1 $Diabetes_1$ $Normal_1$) and whether the sexes were examined combined or separately.

The prevalence of hyperuricaemia was significantly higher in the Total study group females (32.8%) compared to females in the Control group (13.8%) p=0.048. When the Study group was divided according to the category of glucose tolerance, the prevalence of hyperuricaemia was high, particularly in the IGT_1 group (25.5%) and $Diabetes_1$ group (36.6%), contributed to by the high prevalence in females in the IGT_1 and $Diabetes_1$ groups (31.6% and 46.2%, respectively).

CHAPTER 11

EXERCISE STRESS TEST (EST) AT YEAR 1

INTRODUCTION

The significance of impaired tolerance (IGT) lies in its association with an increased risk for the development of NIDDM and macrovascular disease, especially coronary heart disease (NDDG 1979, WHO 1980, 1985, Fuller et al 1980, Keen et al 1965, Stamler R and Stamler J 1979).

Much of the evidence for the increased CHD risk in IGT subjects has been based on resting electrocardiogram (ECG) abnormalities and their predictive power with respect to morbidity and mortality viz. future coronary events and mortality (please refer Chapter 7).

Few reports exist in the literature regarding exercise stress test (EST) and IGT - only three of the fifteen population studies of International Collaborative Group Study examined EST in subjects with asymptomatic hyperglycaemia; in one of these studies viz the Basle study, exercise ECG abnormalities did not appear to be consistently more frequent at higher glucose levels (Da Silva et al 1979 from Stamler R and Stamler J 1979).

This chapter examines exercise test (EST) in a subset of the study subjects at Year 1.

SUBJECTS AND METHODS

SUBJECTS:

At Year 1, 20 of the 128 study subjects (12 males and 8 females) were studied. These were subjects who were classified as IGT a year previously (Year 0) using WHO criteria.

METHODS:

(I) At Year 1, a 75G - OGTT was performed (as described in Chapter 2). According to the results of the OGTT, the subjects were divided into three categories of glucose tolerance, based on WHO criteria viz IGT_1 (8 subjects), $Diabetes_1$ (3 subjects) and $Normal_1$ (9 subjects).

(II) In addition, this subset of the study group had a TREADMILL EXERCISE STRESS TEST (EST) performed at Year 1:

a) The subjects were exercised on the QUINTON 2000 STRESS SYSTEM, using the *graded multi-stage Bruce Protocol* (Bruce RA and Hornstein TR 1969).

Exercise was continued for 3 minutes at each stage. Subjects were encouraged to exercise to their maximum. The test was terminated if the patient developed symptoms of chest pain, fatigue, dyspnoea, claudication, arrythmia, or if marked ST-segment changes occured on the electrocardiogram.

B) (i) Three standard electrocardiographic leads - V_1, avf and V_5 - were continuously monitored by a 3 - channel oscilloscope.

(ii) Twelve standard electrocardiographic leads were continuously recorded on a chart recorder during the last thirty seconds of exercise; two minutes, four minutes and six minutes after exercise; and at any time of any noted arrhythmia or ST-segment changes during or after exercise.

C) ST-segment response was interpreted according to standard criteria. (ST-segment was measured 80 msec from the J-point).

The following ST-segment changes were considered positive:

(i) Horizontal or down-sloping ST-segment depression of 0.1mV or greater, persisting at least 80 msec in the absence of pre-existing ST-segment abnormalities.

(ii) ST-segment elevation of 0.1mV or more than the control tracing in any lead except aVr.

(iii) In the presence of ST-segment depression in the control tracing, additional depression greater than or equal to 0.2mV was required.

A test was considered negative only when a subject had achieved 85% of the maximum heart rate predicted and did not have positive ST-T changes.

The predicted maximum heart rate was determined by subtracting the patient's age from 220 i.e.

220 - patient's age = predicted maximum heart rate.

RESULTS

The results have been summarised in Table 1 and 2

1. A positive exercise stress test (EST) was demonstrated in 4 of the 20 study subjects examined (20%); of these 1 was male and 3 female.

   Of the subjects with positive EST, only 1 subject had symptoms of angina; all 4 subjects demonstrated resting ECG abnormalities ("possible" IHD) indicative of IHD, based on Whitehall criteria.

   Of the 16 subjects with negative EST, 11 were male and 5 females; a history of angina and myocardial infarction was obtained in 1 of these 16 subjects (the same patient); 6 of the subjects with a negative EST had resting ECG abnormalities indicative of IHD (4 subjects had "Possible" IHD; 2 subjects had "Probable" IHD).

2. When the subjects were divided according to the category of glucose tolerance at Year 1 (viz IGT_1 $Diabetes_1$ $Normal_1$), positive EST was found in 25% of the IGT_1 group (2 of 8 subjects), 33.3% of the $Diabetes_1$ group (1 of 3 subjects) and 11% of the $Normal_1$ group (1 of 9 subjects).

   Of the 4 subjects with positive EST, 50% (2 subjects) belonged to the IGT_1 group, and 25% each to the $Normal_1$ group and $Diabetes_1$ group.

Table 1

CLINICAL CHARACTERISTICS AND EXERCISE STRESS TEST (EST)
RESULTS IN 20 STUDY SUBJECTS AT YEAR 1

NUMBER	20
*SEX	
Male	12 (60%)
Female	8 (40%)
+AGE (yrs)	43.7 (20-65)
*HISTORY OF IHD:	
Angina	1 (5%)
Myocardial infarct	1 (5%)
*GLUCOSE TOLERANCE:	
IGT	8 (40%)
Diabetes	3 (15%)
Normal	9 (45%)
*EXERCISE STRESS TEST (EST)	
Positive	4 (20%)
Negative	16 (80%)

* number (%)
+ Mean ± SE (Range)

Table 2

CLINICAL CHARACTERISTICS BASED ON EXERCISE STRESS TEST (EST) RESULTS IN 20 STUDY SUBJECTS AT YEAR 1

	EXERCISE STRESS TEST RESULT	
	*Positive	*Negative
NUMBER	4	16
SEX		
Male	1 (25%)	11 (68.7%)
Female	3 (75%)	5 (31.3%)
+MEAN AGE (years)	50.8 (47-54)	41.9 (20-65)
HISTORY OF IHD:		
Angina	1 (25%)	1 (6.3%)
Myocardial infarct	0	1 (6.3%)
RESTING ECG FINDINGS:		
"Possible" ischaemia	4 (100%)	4 (25%)
"Probable" ischaemia	0	2 (12.5%)
Normal	0	10 (62.5%)
GLUCOSE TOLERANCE:		
IGT	2 (50%)	6 (37.5%)
Diabetes	1 (25%)	2 (12.5%)
Normal	1 (25%)	8 (50%)

* number (%)
+ Mean ± SE (range)

DISCUSSION

The significance of IGT lies in its association with an increased risk for the development of NIDDM and macrovascular disease, especially coronary heart disease (NDDG 1979, WHO 1980, 1985, Fuller et al 1980, Keen et al 1985, Stamler R and Stamler J 1979).

Much of the work done on IGT and its association with macrovascular disease (CHD) has been based on historical information of angina and myocardial infarction, resting ECG changes suggestive of ischaemic heart disease, prospective studies examining mortality from CHD in subjects with IGT, and the association of IGT with other known risk factors for CHD (viz blood pressure, obesity, lipid abnormalities).

Few reports exist in the literature, regarding exercise stress test (EST) and IGT - only three of the 15 population studies of the International Collaborative Group Study examined EST in subjects with asymptomatic hyperglycaemia; in one of these studies viz the Basle Study, exercise ECG abnormalities did not appear to be consistently more frequent at higher glucose levels (Da Silva et al 1979 from Stamler R and Stamler J 1979).

The exercise stress test is reported to be a non-invasive reproducible method to assess the presence and extent of anatomic disease, and prognosis, when significant disease has been defined (Mc Neer et al 1978). However, the EST has received much attention in recent years, with the principal focus of interest being its predictive power: in asymptomatic individuals, those with an abnormal ECG response during exercise have been found to have a substantially higher risk of developing manifest CHD than those with a normal ECG response; similarly, many investigators have shown that amongst subjects with chest pain and a normal resting ECG, an abnormal ECG response during stress correlates with anatomically significant disease on subsequent catheterisation; those with a normal ECG response during stress have been found to have a lower probability of significant coronary artery obstruction (Mc Neer et al 1978).

However, the EST has been criticised because of a relatively high incidence of false positives, and more worrying, false negative results. The false positive rate of EST varies principally as a function of age and sex of the population tested and whether the test is employed primarily to screen an asymptomatic population, or to assess functional status in patients with a strong probability of CHD based on other criteria viz. typical angina, previous myocardial infarct.

Whilst by and large, the prime use of EST is as an aid in establishing an aetiologic diagnosis in patients with chest pain, amongst its many other clinical uses is the detection of myocardial ischaemia in subjects at high risk for CHD. It has been reported in a recent review, that the use of EST in asymptomatic individuals who are not at high risk for CHD (i.e. those without a history of smoking, hypertension, diabetes or family history of CHD) is not generally recommended because of the low yield of true positives and the high incidence of false positive tests (Goldschlager N and Sox HC 1988); however no mention was made as to whether IGT subjects are included in this "high-risk" category, although from the studies quoted above, it would have to be accepted that IGT is indeed a risk factor for CHD.

Several studies have addressed the prognostic value of abnormal EST in healthy individuals (Bruce RA and Mc Donough JR 1969, Aronow WS and Cassidy J 1975, Froelicher et al 1974, Allen et al 1980, Mc Henry et al 1984). In these studies the incidence of CAD (documented by the development of angina, acute myocardial infarct or sudden death) during a mean follow-up period of 6 years averaged only 5.2% in those with positive EST, despite a 3.6 - 5.5 fold increase in risk over subjects with normal EST; it is important to note however, that the prevalence of CAD documented angiographically could well have been higher than that of ischaemic events.

The variability in reported results of the prevalence of CAD in asymptomatic subjects, and the predictive value of the EST is explained by the non-uniform patient populations studied. Few reports included women or analysed data by age and sex and not all studies have considered the contributory effect of the presence or absence of associated risk factors. In an 8 year follow-up study of healthy middle-aged aviators, it was found that patients without risk factors but an abnormal EST had a 20% probability of developing clinical CHD (angina, myocardial infarct, sudden death); in patients with one or more associated risk factors and an abnormal EST, the probability increased to 28%. (MacIntyre et al 1981). In another study of asymptomatic men aged 35-55 years, the 5 year probability of a primary cardiac event of those subjects with abnormal EST, increased from 0.0086 in those with no associated risk factor to 0.41 in those with associated risk factors (Bruce et al 1980).

Thus EST may be a reasonable policy in asymptomatic individuals in "high-risk" category, but the yield appears to be small. However, the lack of data on the benefit of medical or surgical therapy in subjects with an abnormal EST, precludes a definitive decision as to the need for EST at the present time (Gold Schlager N and Sox HC 1988).

The finding in the present study that 20% of the study subjects had positive EST would appear to reflect a high prevalence of CHD in those subjects with IGT. The lack of data regarding the prevalence of EST abnormalities in other population groups with IGT precludes comparison. Of interest in the present study was that all those subjects with positive EST demonstrated abnormalities indicative of IHD on resting electrocardiogram. Notwithstanding these observation, caution has to be exercised in reaching any definite conclusions since the small sample size and the lack of control subjects, are obvious shortcomings in interpreting the results. Clearly, what is required is a study which includes a larger number of study subjects as well as control subjects; moreover, of greater value, would be a prospective analysis to determine the predictive power of EST in IGT subjects.

In the light of the foregoing information, several important issues need to be addressed viz. the value of performing EST in asymptomatic individuals; whether the positive EST is a true reflection of the prevalence of anatomically significant CAD; and if a positive EST is found, what recommendations are to be made with respect to further investigations (viz coronary angiography) and / or management of such subjects.

CHAPTER 12

HLA CLASS I AND II ANTIGENS IN THE STUDY GROUP

INTRODUCTION

From studies documented thus far, it has been demonstrated that subjects with IGT are at risk for the development of NIDDM; the proportion of subjects progressing to NIDDM over a 10-year period varying from 13%-52% with a rate of progression of 1%-5% per year (NDDG 1979).

South African Indians, like other migrant Asian Indians, have been shown to have a high prevalence of NIDDM; the prevalence of IGT being 5.8% (Omar et al 1985). The present study has demonstrated that over 50% of such subjects with IGT progressed to NIDDM over a 4-year period.

It has been questioned whether IGT is a separate disease entity (since a proportion return to normal glucose tolerance), or whether it is one end of the whole spectrum of NIDDM (Stern et al 1985).

Whilst there have been studies on the relationship between NIDDM and HLA antigens (Omar et al 1988), to date there appears to be no information on whether a relationship exists between IGT and HLA antigens, and if so, whether the relationship is similar to that between NIDDM and HLA antigens.

This study was therefore undertaken to evaluate the relationship between HLA class I and II antigens in a subset of the study group.

SUBJECTS AND METHODS

SUBJECTS

Of the 128 study subjects, 30 subjects (18 males and 12 females) were studied; these were subjects classified as IGT based on WHO criteria in the baseline study (Year 0).

HLA class I antigens were evaluated in all 30 subjects, and HLA class II antigens in 23 subjects (13 males and 10 females).

The control group comprised 1665 subjects all of whom were typed for HLA class I antigens; for the class II antigens, HLA DR antigens were determined in 606 control subjects and HLA DQ antigens in 370 control subjects. The control group comprised randomly selected staff and blood donors, many of who have been typed for international histocompatibility workshops.

METHODS

The HLA class I antigens (HLA A, B and C) were determined by means of a *two-stage microlymphocytotoxicity test* (Terasaki PI and Mc Clelland JD 1964) with 180 antisera. They consisted of local sera that have been requested for use in International Histocompatibility Testing Workshops, local sera that have been verified with International Workshop sera, and sera that have been exchanged with other laboratories worldwide.

HLA DR antigens were determined by means of a *microlymphocytotoxicity test* using B cell-enriched lymphocyte suspensions prepared with the aid of straws packed with cotton wool (Danilovs et al 1980).

The definition of B60 with operationally monospecific antisera is clear, but the definition of B61 depends on the difference in reaction patterns between the broad antigens B40 and B60 (Goldmann et al 1984; 1984). This means that it is not possible to detect B61 in the presence of B60, and therefore subjects with both B60 and B61 were counted as having B60 and a "blank", resulting in an underestimation of the frequency of B61. However, the antigen frequency was not modified because there are many other cross-reacting groups where antigen may be "hidden" eg A10, B5, B15, and further corrections would have been necessary to allow for homozygosity.

STATISTICAL ANALYSIS

Differences in HLA frequencies were tested for significance with the X^2 test (without Yates' correction), and the probability was corrected (Pc) by multiplying the p values by the number of comparisons made, i.e., the number of different antigens tested (Svejgaard et al 1974).

Relative risk (RR) was calculated according to the formula recommended by Woolf (Woolf B 1955)

$$RR = \frac{\text{number of patients positive} \times \text{number of controls negative}}{\text{number of patients negative} \times \text{number of controls positive}}$$

$$\text{ie. } RR = \frac{\text{no. of patients +ve} \times \text{no. of controls -ve}}{\text{no. of patients -ve} \times \text{no. of controls +ve}}$$

RESULTS

Results shown in Table 1-3

HLA class II antigens:

Table 1.

No significant difference in the frequencies of any of the HLA class II antigens (at DR and DQ locus) was observed between the study group and the control group.

HLA class I antigens:

Table 2 and 3.

At the A locus, there was no significant difference in the frequency of any of the antigens between the study and control group.

There was a significant increase in the frequency of B41 in the study group compared with the control group (21.8% vs 6.7%, Pc 0.0000, RR 16.9).

The frequency of B60 was higher in the study group compared to the control group (26.67% vs 9.37%, p = 0.0015); however, the corrected p value fell short of statistical significance (Pc 0.07).

No significant difference was observed between the study and control groups, for the frequency B61.

The frequencies of subgroups of HLA B40 are shown in Table 3. When the study group was compared to the control group, there was a 15 - fold increase in the frequency of B41 and a 3-fold increase in the frequency of B60, although a significant difference was only observed for B41 (Table 2).

Table 1

FREQUENCY OF HLA CLASS II ANTIGENS IN STUDY GROUP AND CONTROL GROUP

ANTIGEN	FREQUENCY (%)	
	CONTROL GROUP (n=606)	STUDY GROUP (n=23)
DR1	5.3	8.7
DR2	39.8	43.5
DR3	11.4	17.4
DR4	19.9	26.1
DR5	17.5	13.0
DR6	14.7	0.0
DR7	28.6	43.5
DR8	7.6	0.0
DR9	0.5	0.0
DR10	9.9	13.0
DQw1	72.2	82.6
DQw2	21.6	17.4
DQw3	37.3	39.1

Table 2

FREQUENCY OF HLA CLASS I ANTIGENS IN STUDY GROUP AND CONTROL GROUP

ANTIGEN	FREQUENCY (%)		ANTIGEN	FREQUENCY (%)		ANTIGEN	FREQUENCY (%)	
	CONTROL GROUP (n=1665)	STUDY GROUP (n=30)		CONTROL GROUP (n=1665)	STUDY GROUP (n=30)		CONTROL GROUP (n=1665)	STUDY GROUP (n=30)
A1	28.7	16.7	B7	13.9	13.3	B51	15.7	13.3
A2	30.6	40.0	B8	4.7	3.3	B52[c]	14.5	0.0
A3	12.7	13.3	B13	6.4	10.0	B53	0.3	0.0
A11	26.9	20.0	B14[a]	0.5	3.3	B51	2.8	0.0
A23	1.6	0.0	B18	2.8	3.3	B57	12.1	3.3
A24	30.4	36.7	B21	3.4	6.7	B58	9.1	13.3
A25	0.9	0.0	B22	5.2	3.3	B60[d]	9.4	26.7
A26	5.9	3.3	B27	2.5	3.3	B61	17.6	6.7
A28	12.8	16.7	B35	21.1	26.7	B62	6.4	13.3
A29	1.7	0.0	B37	5.7	3.3	B63	4.9	0.0
A30	1.8	3.3	B38	1.9	0.0	B70	5.9	13.3.
A31	4.7	0.0	B39	1.6	0.0			
A32	4.2	6.7	B41[b]	0.4	6.7			
A33	13.8	10.0	B42	0.1	0.0			
A34	0.1	0.0	B44	13.2	10.0			
A36	0.1	0.0	B45	0.2	0.0			
A43	0.0	0.0	B47	0.2	0.0			
A66	0.4	0.0	B48	0.1	0.0			

Note. puc = p uncorrected; pc = p corrected; RR = relative risk.

[a]puc = 0.03; ; pc = 1.6 ; RR 7.1

[b]puc = 0.0000 ; pc = 0.0000 ; RR 16.9

[c]puc = 0.02 ; pc = 1.1 ; RR 0.0

[d]puc = 0.0015 ; pc = 0.07 ; RR 3.5

Table 3

FREQUENCY OF SUBGROUPS OF HLA B40 ANTIGEN IN STUDY AND CONTROL GROUPS

ANTIGEN	*CONTROL GROUP n (%)	*STUDY GROUP n (%)	puc	pc	RR
B60	156 (9.4%)	8 (26.7%)	0.0015	0.07	3.5
B61	293 (17.6%)	2 (6.7%)	ns	ns	0.3
B48	2 (0.1%)	0 (0%)	ns	ns	0.0
B47	4 (0.2%)	0 (0%)	ns	ns	0.0
B41	7 (0.4%)	2 (6.7%)	0.0000	0.00	16.9
B13	106 (6.4%)	3 (10.0%)	ns	ns	1.6

Note : puc = p uncorrected ; pc = p corrected ; RR = relative risk
* Control group : total number tested = 1665
Study group : total number tested = 30

DISCUSSION

There appears to be strong evidence for the role of a genetic component in the aetiology of NIDDM, as demonstrated by the high concordance for NIDDM in monozygotic twins (Pyke DA 1979, Barnett et al 1981, Zimmet et al 1990, Serjeantson SW and Zimmet P 1989) and by abnormal glucose tolerance in more than 30% of siblings of patients with NIDDM (Köbberling et al 1982, O'Rahilly et al 1987, Serjeantson et al 1984).

Studies addressing the genetics of NIDDM have employed two approaches viz. pedigree analysis (family studies) and the analysis of genetic markers (Zimmet et al 1990). Several studies have reported associations between NIDDM and a range of genetic markers which include HLA, blood group, and serum protein markers, as well as "candidate genes" for a primary inherited defect viz. insulin, insulin-receptor and the erythrocyte-type glucose transporter gene (Serjeantson SW and Zimmet P 1989).

With the introduction of the category of IGT and the appeal for population based studies on IGT it was hoped that such studies might shed light on the validity of IGT as a discrete entity, and may provide further evidence regarding the pathogenesis of NIDDM (NDDG 1979, WHO 1980, 1985). Subsequent to its introduction, prospective studies have demonstrated variable rates for the risk of subsequent progression (worsening) to NIDDM in subjects with IGT, and it has been questioned whether IGT is a separate disease entity (since a proportion return to normal glucose tolerance) or whether in fact it is just one end of a continuum of glucose intolerance (Stern et al 1985, Dowse GK and Zimmet P 1989, Zimmet et al 1990, Yudkin et al 1990). The argument for genetic studies in IGT subjects is that such studies may be one way of addressing this question.

Several studies have examined the relationship between NIDDM and HLA antigens in various population groups, although the evidence for any relationship appears inconsistent (Serjeantson SW and Zimmet P 1989, Omar et al 1988). To date however, there appears to be a lack of reported studies on whether a relationship exists between IGT and HLA antigens, and if it does, whether such a relationship is similar to that between NIDDM and HLA antigens.

As regards NIDDM and HLA class I antigens, studies have highlighted a paucity of any such relationship in Caucasians (Tiwari JL and Terasaki PI 1985, Rotter and Rimoin DL 1979, Platz et al 1982, Arnaiz Vellena et al 1980). Data from other populations appear to indicate that NIDDM may be characterised by differences in the specific allelic associations among various ethnic groups viz. an increased frequency of A2 in Pima Indians (Williams et al 1981), of B54 in Chinese (Zhao et al 1982), of B22 in Micronesians and Polynesians (Serjeantson et al 1982), of Bw62 (B15) in Papuans (Bhatia et al 1984), and of Bw41 in South African Xhosas (Briggs et al 1980). An association between NIDDM and HLA Bw61 has been observed in two migrant Asian Indian groups viz the Fiji Indians (Serjeantson et al 1981) and South African Indians (Omar et al 1988).

With respect to NIDDM and HLA class II antigens, no consistent relationship has been shown in Caucasians (Tiwari JL and Terasaki PI 1985); in the only two reported studies on migrant Asian Indians, no association was found between NIDDM and HLA DR antigens (Serjeantson et al 1981, Omar et al 1988).

Since published data on the relationship between IGT and HLA antigens are not available, comparison with other studies is not possible. The present study has demonstrated no association between IGT and HLA class II antigens (DR and DQ loci). As regards class I antigens, the study group demonstrated a significant increase in the frequency of B41 and B60, although for the latter, the Pc fell short of statistical significance (p0.07). HLA B41 is a rare antigen and can be confused with subgroups of B40 (B60, B61, B47, B48, B41, B13).

The significance, if any, of these findings is at present unclear, especially in view of the small sample size; however, it does appear that if any association exists between IGT and HLA antigens, it is at B - locus, and in particular HLA B40 and its subtypes. Clearly, what is required, are further studies with larger subject numbers; moreover, it needs to be determined whether IGT subjects destined to progress to NIDDM possess different HLA antigens from those subjects who do not progress.

If on the other hand, IGT is just one end of a spectrum of glucose intolerance (ie. diabetes), then the findings in the present study may be compared to other studies on NIDDM and its association with HLA antigens, in particular those on migrant Asian Indians. In the studies on Fiji Indians and South African Indians, although an association was found between NIDDM and HLA B40, the sub-type involved was different ie. B61 and not B60 as found in the present study; and neither of those studies demonstrated an increased frequency of HLA B41.

That there was a lack of an association with B61 in the present study, could be explained by the definition of B61 which depends on the difference in reaction patterns between the broad antigen B40 and B60, resulting in an underestimation of the frequency of B61 in those patients with both B60 and B61, since such patients would be labelled as having B60 and a "blank".

The observation in the present study, of an increased frequency of B41 in the study subjects, is at variance with those of the Fijian and South African Study, in which no association was found. A weak association between HLA B41 and NIDDM has been previously reported in South African Xhosas (Briggs et al 1980).

However, the results of the present study should be viewed with caution because of the small number of subjects studied.

In summary therefore, the findings in the present study of an increased frequency of HLA B41 and B60, suggests that irrespective of whether IGT is a discrete entity or not, the only association between IGT and HLA antigens appears to be at the B locus, in particular sub-types of HLA B40, but further studies are certainly needed to verify these findings.

CHAPTER 13

RISK FACTORS FOR PROGRESSION TO DIABETES MELLITUS (NIDDM) IN STUDY SUBJECTS

INTRODUCTION

Subjects with IGT have been found to be at a high risk for the development of diabetes mellitus (O'Sullivan and Mahan 1968, Hamman et al 1978, Jarrett et al 1979, Birmingham Diabetes Survey Working Party 1970, 1976, Bennett et al 1982, Jarrett et al 1984, Keen et al 1982, Sazaki et al 1982, King et al 1984, Kadowaki et al 1984, Sartor et al 1980, Saad et al 1988, Schrantz AG 1989) and macrovascular disease (Fuller et al 1980, Jarrett et al 1982, Jarrett and Keen 1976), and therefore constitute a possible target group for intervention (Bennett PH 1985, Saad et al 1988).

From reported studies, the proportion of individuals with IGT which progresses to NIDDM over varying periods varies from 13% - 52% with a rate of progression of 1% - 5% per year (Table 1, NDDG 1979).

A prospective study of the natural history of IGT is a useful way to determine the significance of IGT with respect to its pathophysiological mechanisms and prognostic implications in different populations; moreover, a prospective study allows for examination of risk factors predictive of subsequent development to NIDDM in subjects with IGT.

However, few reports on prospective studies on IGT exist in the literature (primarily from the UK, U.S, Japan and Nauru - see above), and it is therefore not surprising that there has been a call from the WHO Expert Committee on Diabetes (1980, 1985) for further population based studies of IGT, in an attempt to shed light on the validity of this entity, as well as to provide evidence concerning the present diagnostic criteria for glucose tolerance.

To date, there have been no published reports on prospective studies of IGT in migrant Asian Indians.

South African Indians, a migrant Asian Indian group, have been found to have a high prevalence of diabetes mellitus, the prevalence of IGT being 5.8% (Omar et al 1985).

The present study which prospectively examined IGT subjects has demonstrated that 50.4% of these subjects progressed to NIDDM over a four year period. (please refer Chapter 5).

This chapter examines the risk factors associated with progression to diabetes mellitus in South African Indian subjects with IGT (study subjects).

Table 1

PROGRESSION (WORSENING) TO DIABETES AND ASSOCIATED RISK FACTORS IN PROSPECTIVE STUDIES ON IGT

STUDY	% PROGRESSING TO DIABETES	[a]RISK FACTORS (PREDICTORS) FOR PROGRESSION
UK:		
WHITEHALL (Jarrett et al 1979,	13.2	gluc*
1984	29.4	gluc⁺, ↓SBP, ↓Tg
BEDFORD (Keen et al 1982)	15.0	gluc⁺, BMI
BIRMINGHAM (1970	21.4	gluc*
1976)	45.0	
USA:		
WHITES (O'Sullivan and Mahan 1968)	52.5	gluc (0min, postload), weight
**PIMA INDIANS:		
(Knowler et al 1986)	27.0-5yr 48.0-10yr	gluc⁺, age, ins§
(Saad et al 1988)	31.0	gluc*, age, ins§
JAPAN:		
OSAKA (Sazaki et al 1982)	38.5	gluc*
TOKYO (Kadowaki et al 1984)	16.7	gluc*, BMI, ins (↓½hr)
SWEDEN (Sartor et al 1980)	29.0	
*NAURU (King et al 1984)	26.0	gluc*
*MALTA (Schranz AG 1989)	31.0	gluc*, age, BMI

**WHO criteria employed

[a] baseline variables:

- gluc - blood glucose
- SBP - systolic blood pressure
- Tg - plasma triglyceride
- ins - insulin
- BMI - body mass index

*fasting + 2hr post load level

⁺2hr level only

§↑fasting, ↓2hr post load level

SUBJECTS AND METHODS

SUBJECTS

BACKGROUND

(Please refer to Chapter 2, 3a, 4, 5:
Figure 1 and 2, Table 1 from Chapter 5).

A. As described in Chapter 2, in an epidemiological survey in 1984 (Year 0), 143 subjects were diagnosed as IGT based on WHO criteria. Of these **128** subjects (67 males and 61 females) consented to participate in a prospective study from September 1985 - December 1988 (Year 1 - Year 4 of present study) - these subjects constituted the *STUDY GROUP* in the present study.

I. Of the 128 subjects (study group) who entered into this prospective study at Year 1, **113** subjects satisfactory completed the study by Year 4, either by returning for follow-up OGTT (those who were IGT_1 or $Normal_1$) or because they had reached the end-point of the study (date of diagnosis of NIDDM at any point) - the response rate was 88.3%.

By Year 4, 57 subjects **(50.4%)** had *progressed* to NIDDM, 28 subjects **(24.8%)** *persisted* with IGT and 28 subjects **(24.8%)** had *reverted* to Normal glucose tolerance. The rate of progression to NIDDM was 12.6% per annum.

II. At Year 1 of the study, 47 subjects were diagnosed as IGT - these constituted the IGT_1 group. Of these, 40 subjects satisfactorily completed the study - the response rate was 85%. By Year 4, the fate of this group was as follows:-

16 subjects (40%) *progressed* to NIDDM, 17 subjects (42.5%) *persisted* with IGT and 7 subjects (17.5%) *reverted* to Normal glucose tolerance. Thus the rate of progression to NIDDM in the IGT_1 group was 13.3% per year.

B. In the original study (Year 0), which was a field study, a modified OGTT was performed (fasting and 2hr post plasma glucose), heights and weights were measured (for BMI), and details of family history were obtained in all subjects. A subset of the subjects had blood pressure examination and assessment of plasma insulin during OGTT. A detailed description of the clinical and biochemical profiles was not the purpose of that study.

However, the present study (Year 1 - Year 4 inclusive) entailed a more detailed clinical and biochemical examination of the study subjects (please refer to Chapter 2, 3a and 4).

Examination of risk factors predictive of progression to NIDDM in IGT subjects necessitates an analysis of baseline variables. In the light of the foregoing information therefore, the study for risk factors was divided into two aspects, viz:

I. Year 0 as baseline - for the 113 IGT_0 subjects.

II. Year 1 as baseline - for the 40 IGT_1 subjects.

METHODS

The methods have been described in detail in Chapter 2, 3a 4 and 5 Briefly,

I. **Year** 0 as baseline - for the 113 IGT_0 subjects, baseline variables which were analysed included age, sex, family history of diabetes in first degree relatives, BMI, fasting and 2hr postload plasma glucose during OGTT; in a subset of patients, blood-pressure (53 subjects), fasting and 2hr plasma insulin during OGTT (16 subjects) and Insulinogenic $Index_{120}$ (11 subjects) were analysed.

II. **Year** 1 as baseline - for the 40 IGT_1 subjects, the baseline variables which were analysed included age, sex, family history of diabetes in first degree relatives, BMI, blood pressure, plasma glucose and insulin during OGTT (0, 15, 30, 60, 90 and 120 min), Insulinogenic Index (15 and 120 min), Insulin Area, Insulin Ratios, fasting serum Total Cholesterol and Total Triglyceride, Glycosylated Haemoglobin (HbA_1) and plasma uric acid.

STATISTICAL ANALYSIS

Statistical analyses were performed with programs of the SAS Institute. For the univariate analysis, three group comparisons were performed by analysis of variance or chi-square method; 2 group comparisons were performed by t-test and chi-square method. (SAS Institute 1988).

For the multivariate analysis, to evaluate the effect of various risk factors (predictor variables), the multiple logistic regression model was used to predict progression to diabetes. Selection of variables was done in a stepwise fashion with the use of a **backward elimination method.** (Armitage P and Berry G 1987).

RESULTS

Results are summarised in Table 2 - 10, Figure 1 - 3.

I. RISK FACTORS ASSOCIATED WITH PROGRESSION TO NIDDM WITH YEAR 0 AS BASELINE (113 IGT_0 SUBJECTS)

Table 2, 3, 6, 8, 9 Figure 1 and 2

A. UNIVARIATE ANALSYSIS

To assess which factors were associated with subsequent progression to diabetes in subjects with IGT, the means of selected baseline clinical and biochemical variables (Year 0) were compared in the group which progressed to diabetes (Group 1) to the group which did not progress to diabetes (Group 2) (Table 2).

There was a significant difference between the two groups for the following variables: sex (p 0.047), BMI (p 0.0019), obesity (p 0.012), fasting plasma glucose (p 0.004), 2hr plasma glucose (p 0.0001) and diastolic blood pressure (p 0.0035).

The Mean BMI was significantly higher in Group 1 compared to Group 2 (27.03 vs 24.45, p 0.0019), the prevalence of obesity being 51.79% and 28.57%, respectively (p 0.012). The mean fasting plasma glucose (5.71 mmol/L vs 5.01 mmol/L, p 0.0004) and mean 2hr plasma glucose (9.39 mmol/L vs 8.58 mmol/L, p 0.0001) were significantly higher in Group 1 compared to Group 2.

In 53 subjects in whom blood pressure data was available, the mean diastolic blood pressure in Group 1 was 90.77 mmHg compared to Group 2, 80.39 mmHg, with a significant difference between the two groups, p0.0035.

No significant difference was observed between the two groups for the other variables analysed (age, family history of diabetes, systolic blood pressure, plasma insulin and Insulinogenic Index).

The trend in the proportion of subjects progressing to diabetes across quartiles and quintiles of baseline plasma glucose concentration (both fasting and 2hr levels) is tabulated and illustrated in Table 8 and 9, Figure 1 and 2.

The rate of progression to diabetes increased with increasing baseline plasma glucose, both fasting and 2hr levels.

As regards baseline fasting plasma glucose (FBG) levels, 100% of those subjects who had FBG ≥ 7.3 – < 7.8 mmol/L at Year 0, progressed to diabetes by the end of the study period (Table 9, Figure 1).

None of the subjects who had 2hr plasma glucose < 7.9 mmol/L at Year 0 progressed to diabetes, whilst 100% of those subjects with levels ≥ 10.2 mmol/L progressed to diabetes.

Table 2

BASELINE VARIABLES (YEAR 0) IN RELATION TO PROGRESSION TO DIABETES IN 113 IGT_0 SUBJECTS

*VARIABLE (CHARACTERISTIC)	PROGRESSING TO DIABETES (n=57)	NOT PROGRESSING TO DIABETES (n=56)	p
Age (yr)	49.59	46.36	0.17
Sex (M/F)	25/32	35/21	0.047
Family history of diabetes (%):	53.6	44.6	0.4
Father only	17.86	12.73	0.4
Mother only	32.14	25.45	0.7
Both parents	10.53	1.79	0.054
Neither parent	61.40	64.3	0.75
Brothers	12.5	20.0	0.4
Sisters	17.86	10.91	0.2
Sons	3.57	0.0	0.2
Daughters	0.0	0.0	-
Body Mass Index (kg/M²)	27.03	24.45	0.0019
[d] Obese (%)	51.79	28.57	0.012
[a] Blood pressure (mm/Hg):			
Systolic	139.20	127.65	0.09
Diastolic	90.77	80.39	0.0035
Plasma glucose (mmol/L):			
0 min (fasting)	5.71 (3.3-7.7)	5.01 (2.7-7.2)	0.0004
120 min (2-hr post load)	9.39 (7.9-11.0)	8.58 (7.8-10.1)	0.0001
[b] Plasma insulin (uμ/ml):			
0 min (fasting)	23.14	9.60	0.09
120 min (2-hr post load)	88.34	62.96	0.23
[c] Insulinogenic Index (120 min)	16.83	11.80	0.7

[a] n = 53 subjects only
[b] n = 16 subjects only
[c] n = 11 subjects only
[d] Obesity: BMI ≥ 27 in males
≥ 25 in females

*Mean values except for plasma glucose - Mean (Range)

Figure 1

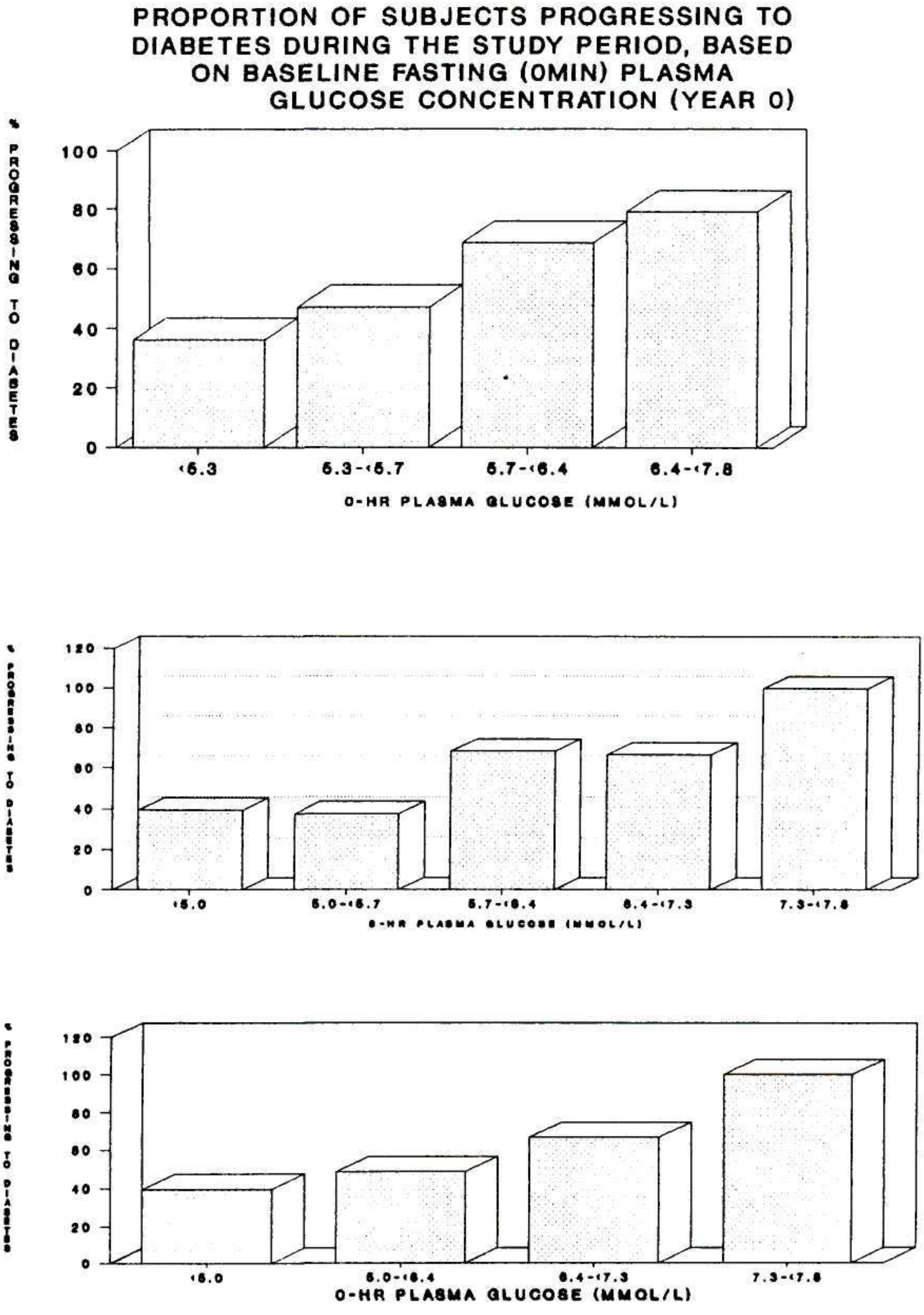
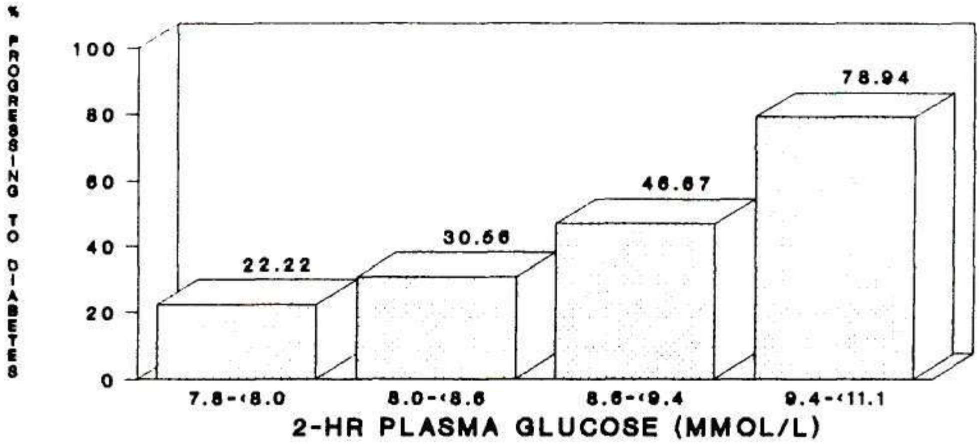
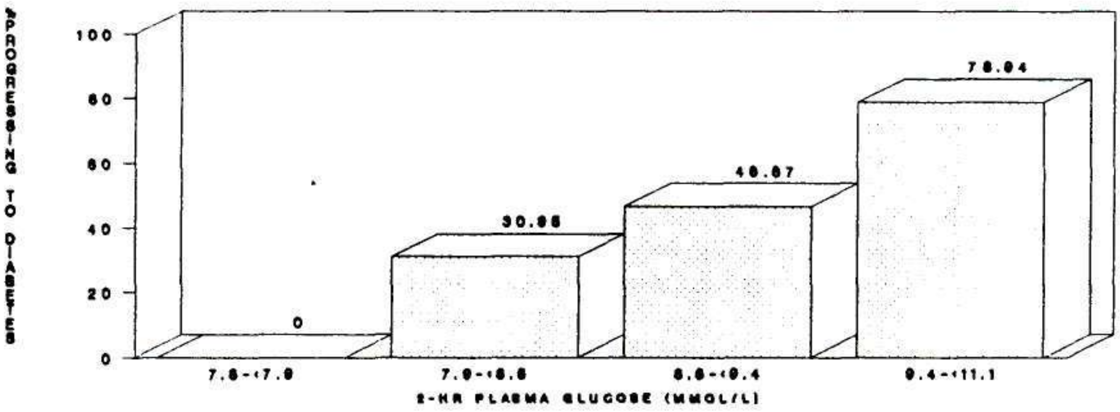
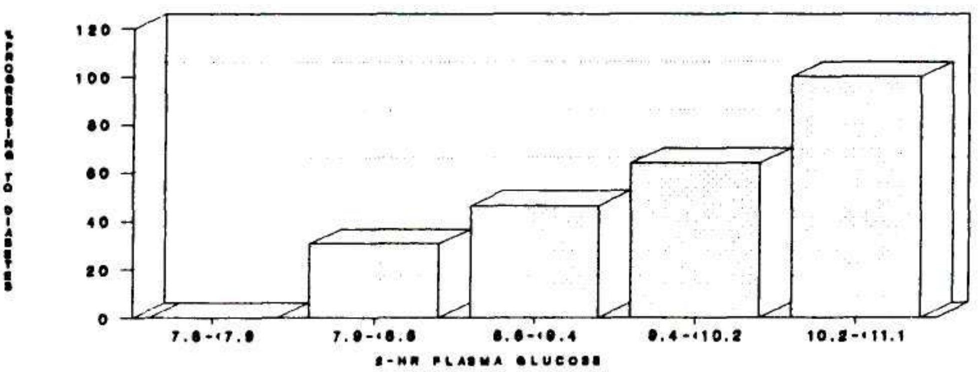

PROPORTION OF SUBJECTS PROGRESSING TO DIABETES DURING THE STUDY PERIOD, BASED ON BASELINE FASTING (OMIN) PLASMA GLUCOSE CONCENTRATION (YEAR 0)
% PROGRESSING TO DIABETES
100
80
60
40
20
0
<5.3
5.3-<5.7
5.7-<6.4
6.4-<7.8
0-HR PLASMA GLUCOSE (MMOL/L)
120
100
80
60
40
20
0
<5.0
5.0-<5.7
5.7-<6.4
6.4-<7.3
7.3-<7.8
120
100
80
60
40
20
0
<5.0
5.0-<6.4
6.4-<7.3
7.3-<7.8
0-HR PLASMA GLUCOSE (MMOL/L)

Figure 2

PROPORTION(%) OF SUBJECTS PROGRESSING TO DIABETES OVER STUDY PERIOD, BASED ON 2HR PLASMA GLUCOSE CONCENTRATION (YEAR O)







B. MULTIVARIATE ANALYSIS

Table 3

To assess their independent contribution to the probability of progression to diabetes, those baseline variables which were significant in the univariate analysis (Table 2) were further examined by means of the multiple logistic regression model (with backward elimination) predicting development of diabetes (Table 3). Diastolic blood pressure was excluded from the multivariate analysis, since data were available on 53 subjects only.

Initially, the four significant baseline variables were used (sex, BMI, fasting and 2hr plasma glucose), and parameter estimates, chi-square and p values were calculated. Subsequently, variables were eliminated one by one in a backward stepwise fashion according to the highest p value (lowest chi-square value).

Fasting and 2hr plasma glucose concentrations were found to be significant predictors of subsequent diabetes in the model. Sex and Body Mass Index, which were significant in the univariate analysis, failed to achieve significance in the multiple regression model i.e. the significant variables in the final model were fasting and 2hr plasma glucose.

The model appeared to fit the data adequately as shown by the likelihood ratio (p0.17) from maximum likelihood analysis of variance.

Table 3

MULTIPLE LOGISTIC REGRESSION MODEL PREDICTING PROGRESSION TO DIABETES IN TOTAL STUDY GROUP (IGT_0): PARAMETER ESTIMATES, STANDARD ERRORS, CHI-SQUARE VALUE AND p VALUES FOR SELECTED VARIABLES (YEAR 0)

VARIABLE	PARAMETER ESTIMATE	STANDARD ERROR	CHI-SQUARE	p
Initial Step:				
Sex	-0.63	0.46	1.85	0.17
Body Mass Index (kg/M^2)	-0.06	0.06	0.92	0.34
0 min plasma glucose (mmol/L)	-0.49	0.24	4.21	0.04
2-hr plasma glucose (mmol/L)	-1.04	0.29	12.80	0.0003
Final Step:				
0 min plasma glucose (mmol/L)	-0.55	0.23	5.83	0.0158
120 min plasma glucose (mmol/L)	-1.08	0.28	14.74	0.0001

II. RISK FACTORS ASSOCIATED WITH PROGRESSION TO NIDDM WITH YEAR 1 AS BASELINE (40 IGT_1 SUBJECTS)

Table 4, 5, 7, 10 Figure 3

A. UNIVARIATE ANALYSIS

Table 4a, 4b, 7, 10 Figure 3

To assess which factors were associated with subsequent progression to diabetes in the 40 IGT_1 subjects, the means of selected clinical and biochemical variables were compared in the group which progressed to diabetes (Group 1) and the group which did not progress to diabetes (Group 2) (Table 4a and 4b).

A significant difference between the two groups was demonstrated for the following variables : history of paternal diabetes (p 0.024) systolic blood pressure (p 0.04). 30 min plasma glucose (p 0.04), 60 min plasma glucose (p 0.0044), and 90 min plasma glucose (p 0.0007).

A positive history of paternal diabetes was significantly higher in Group I compared to Group 2 (31.3% vs 8.3% p 0.024). The Mean systolic blood pressure was significantly higher in Group 1, 138.13 mmHg compared to Group 2, 124.58 mmHg p.0.04. For each of the timed mid-test plasma glucose quoted above, the mean plasma glucose was significantly higher in Group 1 compared to Group 2 : mean 30 min plasma glucose (10.56 vs 9.57 mmol/L p 0.04); mean 60 min (1hr) plasma glucose (12.15 vs 10.43 mmol/L p 0.0044); 90 min plasma glucose (11.72 vs 9.75 mmol/L p 0.0007).

Table 4a

BASELINE CLINICAL VARIABLES (YEAR 1) IN RELATION TO PROGRESSION TO DIABETES IN 40 IGT_1 SUBJECTS

VARIABLE	PROGRESSING TO DIABETES (n=16)	NOT PROGRESSING TO DIABETES (n=24)	p
Age (yr)	48.06	48.88	0.8
Sex (M/F)	9/7	16/8	0.5
Family history of diabetes (%):			
Father only	31.3	8.3	**0.024**
Mother only	43.8	20.8	0.3
Both parents	12.5	0.0	0.08
Neither parent	62.5	29.2	**0.04**
Brothers	25.0	17.39	0.4
Sisters	12.5	17.39	0.4
Sons	0.0	0.0	-
Daughters	0.0	0.0	-
Body Mass Index (Kg/M^2)	26.52	25.35	0.35
Obese (%)	56.25	37.50	0.24
Blood Pressure (mmHg):			
Systolic	138.13	124.58	**0.04**
Diastolic	86.50	77.92	0.06

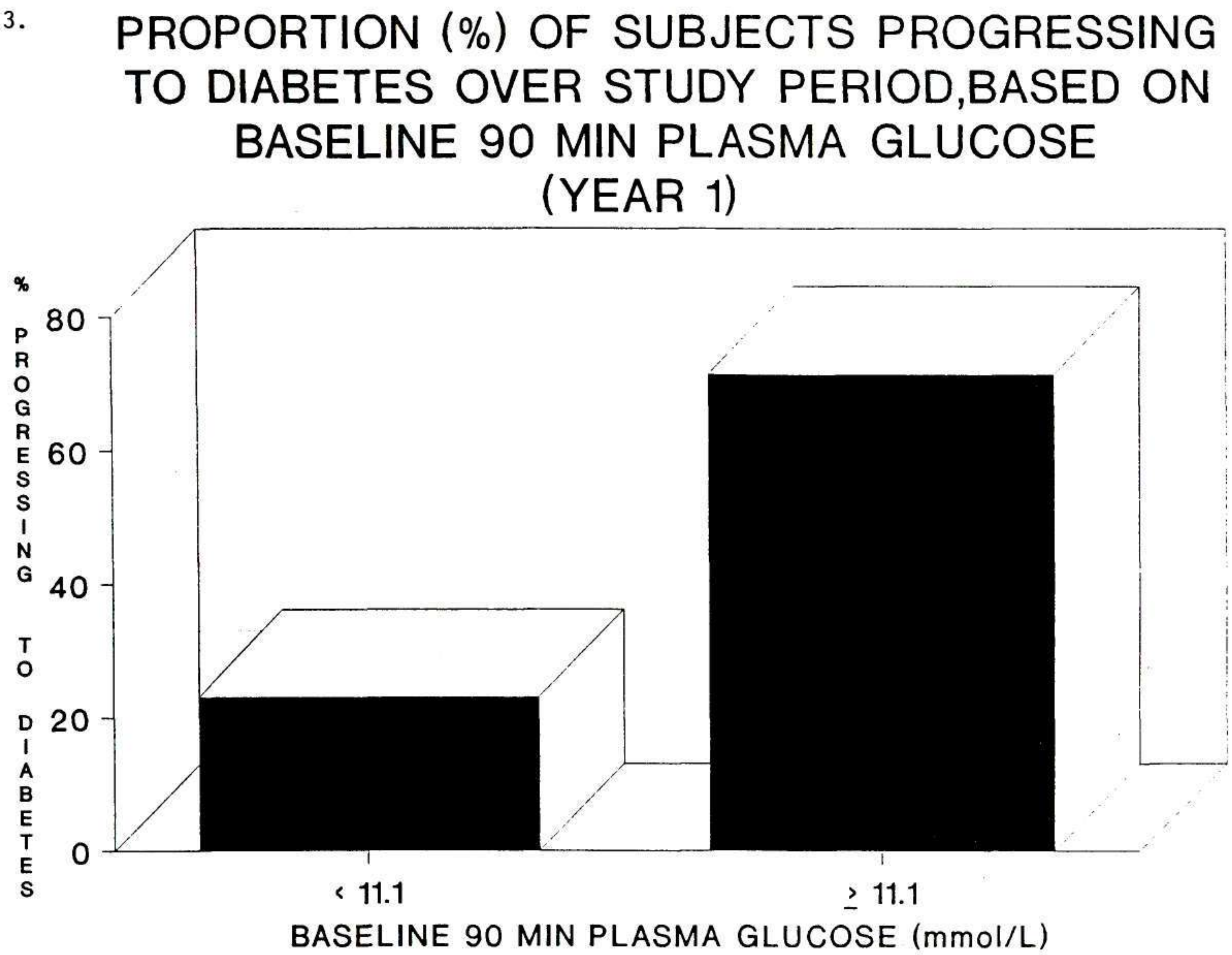
***Obesity : BMI ≥ 27 in males**
≥ 25 in females

Table 4b

MEAN VALUES OF BASELINE BIOCHEMICAL VARIABLES (YEAR 1) IN RELATION TO PROGRESSION TO DIABETES IN 40 IGT_1 SUBJECTS

VARIABLE	PROGRESSING TO DIABETES (n=16)	NOT PROGRESSING TO DIABETES (n=24)	p
Plasma glucose (mmol/L):			
0 min	6.34	6.29	0.8
15 min	7.61	7.45	0.7
30 min	10.56	9.57	0.04
60 min	12.15	10.43	0.0044
90 min	11.72 (9.7-16.3)	9.75 (7.3-14.0)	0.0007
120 min	9.69	9.26	0.17
Plasma insulin (μu/ml):			
0 min	15.63	16.55	0.82
15 min	33.34	43.62	0.2
30 min	57.95	77.45	0.2
60 min	111.20	113.71	0.9
90 min	114.34	127.0	0.6
120 min	121.12	134.03	0.65
Plasma cholesterol (mmol/L)	6.40	6.77	0.4
Plasma Tg (mmol/L)	1.78	2.05	0.34
Plasma uric acid (mmol/L)	0.36	0.38	0.6
Glycated Haemoglobin (%)	7.81	7.39	0.43
Insulin Area (μu/ml hr)	175.93	196.73	0.62
Insulinogenic Index $(\frac{\Delta \text{ insulin}}{\Delta \text{ glucose}})$:			
15 min	22.35	24.69	0.8
120 min	37.04	64.12	0.23
Ratio:			
fasting insulin/glucose	2.39	2.71	0.6
post load insulin/glucose	12.74	14.42	0.6
post load insulin/fasting insulin	9.14	14.55	0.3

Figure 3.


PROPORTION (%) OF SUBJECTS PROGRESSING TO DIABETES OVER STUDY PERIOD,BASED ON BASELINE 90 MIN PLASMA GLUCOSE (YEAR 1)
% PROGRESSING TO DIABETES
80
60
40
20
0
< 11.1
≥ 11.1
BASELINE 90 MIN PLASMA GLUCOSE (mmol/L)

No significant difference was observed between the two groups for any of the remaining numerous clinical and biochemical variables analysed (Table 4a and 4b).

The trend in the proportion of subjects progressing to diabetes, at different cut-off levels for 90 min plasma glucose concentration is demonstrated in Table 10 and Figure 3.

Only 23.08% of those subjects who had 90 min plasma glucose < 11.1 mmol/L at Year 1, progressed to diabetes, whilst 71.4% of those with levels ≥ 11.1 mmol progressed to diabetes.

B. MULTIVARIATE ANALYSIS

As with I; the significant baseline variables examined in the univariate analysis (Table 4a and 4b) were further examined by means of the multiple logistic regression model predicting development of diabetes (Table 5).

The most significant variable in the final model was the 90 min plasma glucose concentration.

Systolic blood pressure, 30 min and 60 min plasma glucose, and a positive history of paternal diabetes which were significant in the univariate analysis failed to achieve significance in the multiple regression analysis model.

Table 5

MULTIPLE LOGISTIC REGRESSION MODEL PREDICTING PROGRESSION TO DIABETES IN 40 IGT_1 SUBJECTS: PARAMETER ESTIMATES, STANDARD ERROR, CHI-SQUARE VALUE AND p VALUES FOR SELECTED VARIABLES (YEAR 1)

*VARIABLE	PARAMETER ESTIMATE	STANDARD ERROR	CHI-SQUARE	p
Initial Step:				
Family history (father only)	0.007	0.91	0.00	0.99
Systolic blood pressure	0.05	0.05	0.72	0.395
Diastolic blood pressure	0.0009	0.07	0.00	0.99
30 min plasma glucose	0.13	0.35	0.13	0.72
60 min plasma glucose	0.32	0.35	0.87	0.35
90 min plasma glucose	0.67	0.36	3.58	0.058
120 min plasma glucose	-0.54	0.55	0.98	0.32
Final Step:				
90 min plasma glucose	0.77	0.28	7.44	0.0064

* blood pressure (mmHg)
plasma glucose (mmol/L)

Table 6

BASELINE CHARACTERISTICS (YEAR 0) OF 113 STUDY SUBJECTS (IGT_0), ACCORDING TO OUTCOME BY YEAR 4

CHARACTERISTIC	CATEGORY OF GLUCOSE TOLERANCE BY YEAR 4			p*
	NIDDM (n=57)	IGT (n=28)	NORMAL (n=28)	
Age (yr)	49.59	47.29	45.43	0.34
Sex (M/F)	25/32	19/9	16/12	0.10
Parental diabetes (%):				
Father only	17.86	7.14	18.5	0.49
Mother only	32.14	25.0	25.9	0.79
Both parents	10.53	0.0	3.57	0.13
Neither parents	61.40	67.86	60.71	0.7
Body Mass Index (Kg/M²)	27.03[A]	25.14[A,B]	23.76[B]	0.0039
[d]Obese (%)	51.79	39.29	17.86	0.011
[a]Blood pressure (mmHg)):				
Systolic	139.20	126.15	129.60	0.24
Diastolic	90.77[A]	81.54[A,B]	78.90[B]	0.013
Plasma glucose (mmol/L)				
0 min (fasting)	5.71[A]	5.02[B]	5.02[B]	0.0019
120 min (2hr post load)	9.39[A]	8.70[B]	8.47[B]	0.0001
[b]Plasma insulin (μu/ml):				
0 min (fasting)	23.14	7.3	13.05	0.42
120 min (2hr post load)	88.34	66.3	61.3	0.69
[c]Insulinogenic Index 120 min	16.83	18.3	5.3	0.79

* p values are for comparison between the three groups by analysis of variance or chi-square method.

[a]n = 53 subjects only

[b]n = 16 subjects only

[c]n = 11 subjects only

[d]Obesity : BMI ≥ 27 in males
≥ 25 in females

A,B : Mean values with the same letter are not significantly different.

Table 7a

BASELINE CLINICAL CHARACTERISTICS (YEAR 1) IN 40 IGT_1 SUBJECTS ACCORDING TO OUTCOME BY YEAR 4

**CHARACTERISTIC	CATEGORY OF GLUCOSE TOLERANCE BY YEAR 4			*p
	NIDDM (n=16)	IGT (n=17)	NORMAL (n=7)	
Age (yr)	48.06	49.65	47.0	0.8
Sex (M/F)	9/7	11/6	5/2	0.7
Parental diabetes (%):				
Father only	30.77	0.0	14.3	0.07
Mother only	46.15	21.43	28.57	0.4
Both parents	12.50	0.0	0.0	0.2
Neither parent	37.50	76.47	57.14	0.07
Body Mass Index (Kg/M^2)	26.52	25.89	24.04	0.4
***Obese (%)	56.25	52.9	0.0	0.031
Blood pressure (mmHg):				
Systolic	138.13	127.65	117.14	0.06
Diastolic	86.50	79.41	74.29	0.1

* p values are for comparisons between the three groups by analysis of variance or chi-square method.

** Mean values

*** Obesity : BMI ≥ 27 in males
≥ 27 in females

Table 7b

BASELINE BIOCHEMICAL CHARACTERISTICS (YEAR 1) IN 40 IGT_1 SUBJECTS ACCORDING TO OUTCOME BY YEAR 4

CHARACTERISTIC (Mean values)	CATEGORY OF GLUCOSE TOLERANCE BY YEAR 4			p
	NIDDM (n=16)	IGT (n=17)	NORMAL (n=7)	
Plasma glucose (mmol/L):				
0 min	6.34	6.25	6.39	0.9
15 min	7.61	7.38	7.63	0.8
30 min	10.56	9.37	10.07	0.07
60 min	12.15^{A}	10.30^{B}	$10.74^{A,B}$	**0.0156**
90 min	11.72^{A}	9.92^{B}	9.31^{B}	**0.0025**
120 min	9.69	9.43	8.84	0.16
Plasma insulin (µu/ml):				
0 min	15.63	15.04	20.24	0.6
15 min	33.34	47.02	35.36	0.3
30 min	57.95	90.88	44.81	0.1
60 min	111.20	132.59	67.86	0.3
90 min	114.34	140.18	94.99	0.5
120 min	121.12	150.74	93.46	0.3
Plasma cholesterol (mmol/L)	6.40^{B}	6.12^{B}	8.34^{A}	**0.0086**
Plasma Triglyceride (mmol/L)	1.78	2.05	2.03	0.6
Plasma uric acid (mmol/L)	0.36	0.37	0.38	0.8
Glycated Haemoglobin (%)	7.81	7.48	7.17	0.6
Insulin Area (µu/ml hr)	175.93	223.27	132.25	0.3
Insulinogenic Index:				
15 min	22.35	27.67	17.47	0.7
120 min	37.04	52.38	92.64	0.3
Ratio:				
fasting insulin/glucose	2.39	2.51	3.20	0.6
post load insulin/glucose	12.74	16.07	10.40	0.3
post load insulin/fasting insulin	9.14	18.12	5.86	0.3

Table 8

PROPORTION OF SUBJECTS PROGRESSING TO DIABETES DURING STUDY PERIOD,BASED ON BASELINE FASTING (0 MIN) PLASMA GLUCOSE CONCENTRATION (YEAR 0)

BASELINE FASTING PLASMA GLUCOSE (mmol/L) QUARTILES OR QUINTILES	NUMBER OF SUBJECTS		% PROGRESSING TO DIABETES
	TOTAL (IGT+N+D)	DIABETES	
< 5.3	58	21	36.21
5.3 - < 5.7	17	8	47.06
5.7 - < 6.4	19	13	68.40
6.4 - < 7.8	19	15	78.95
	113	57	
< 5.0	38	15	39.47
5.0 - < 5.7	37	14	37.84
5.7 - < 6.4	19	13	68.42
6.4 - < 7.3	12	8	66.67
7.3 - < 7.8	7	7	100.0
	113	57	
< 5.0	38	15	39.47
5.0 - < 6.4	56	27	48.21
6.4 - < 7.3	12	8	66.67
7.3 - < 7.8	7	7	100.0
	113	57	

Table 9

PROPORTION (%) OF SUBJECTS PROGRESSING TO DIABETES OVER STUDY PERIOD, BASED ON BASELINE 2-HR (120 MIN) PLASMA GLUCOSE CONCENTRATION (YEAR 0)

BASELINE 2-HR PLASMA GLUCOSE (mmol/L) QUARTILES OR QUINTILES	NUMBER OF SUBJECTS		% PROGRESSING TO DIABETES
	TOTAL (IGT+N+D)	DIABETES	
7.8 - < 8.0	9	2	22.22
8.0 - < 8.6	36	11	30.56
8.6 - < 9.4	30	14	46.67
9.4 - < 11.1	38	30	78.94
	113	57	
7.8 - < 7.9	3	0	0.0
7.9 - < 8.6	42	13	30.95
8.6 - < 9.4	30	14	46.67
9.4 - < 11.1	38	30	78.94
	113	57	
7.8 - < 7.9	3	0	0.0
7.9 - < 8.6	42	13	30.95
8.6 - < 9.4	30	14	46.67
9.4 - < 10.2	22	14	63.64
10.2 - < 11.1	16	16	100.0
	113	57	

Table 10

PROPORTION (%) OF SUBJECTS PROGRESSING TO DIABETES OVER STUDY PERIOD, BASED ON BASELINE 90-MIN PLASMA GLUCOSE CONCENTRATION (YEAR 1)

BASELINE 90 MIN PLASMA GLUCOSE (MMOL/L)	NUMBER OF SUBJECTS		% PROGRESSING TO DIABETES
	TOTAL (IGT+N+D)	DIABETES	
< 11.1	26	6	23.08
≥ 11.1	14	10	71.40

DISCUSSION

A prospective population based study of the natural history of IGT is a useful way to determine the significance of IGT with respect to its pathopysiological mechanisms and prognostic implications in different populations; moreover, such a study would allow for examination of risk factors associated with progression to diabetes mellitus should the risk of the latter be increased in the population studied.

However, few reports on prospective studies on IGT exist in literature, and it is hardly surprising that there has been a call from the Expert Committee on Diabetes (1980, 1985), for further population based studies in an attempt to shed light on the validity of this relatively recently introduced entity.

Prior to the initial call from the WHO (1980), much of the information with respect to IGT emerged from the results of studies in British subjects in the UK (Birmingham, Whitehall, Bedford) and studies on Whites and Pima Indians in the United States (O'Sullivan and Mahan 1968, Hamman et al 1978). Subsequently reports emerged from studies in Nauru, Japan, Sweden, Malta and further studies from the UK and US (Pima Indians). (vide infra).

Previous studies have established that the significance of IGT lies in its association with a higher risk for the development of diabetes mellitus (O'Sullivan and Mahan 1968, Hamman et al 1978, Jarrett et al 1979, Birmingham Diabetes Survey Working Party 1970, 1976, Jarrett et al 1982, Keen et al 1982, Bennett et al 1982, Sazaki et al 1982, King et al 1984, Sartor et al 1980, Saad et al 1988, Schrantz AG 1989) and macrovascular disease (Jarrett RJ and Keen H 1976, Fuller et al 1980, Jarrett et al 1982), and there have been suggestions that this group constitutes a possible target for intervention (Bennett PH 1985, Saad et al 1988).

From reported studies, the proportion of individuals with IGT which progresses to NIDDM varies from 13% - 52% over varying intervals of follow up with a rate of progression of 1% - 5% per year (Table 1, NDDG 1979); using WHO criteria for glucose tolerance (1980, 1985) the proportion ranges from 13.2% (Whitehall Study 1979) to 38.5% (Sazaki et al 1982).

To date there have been no published reports on prospective studies of IGT in migrant Asian Indians. A prospective study on native Asian Indians with IGT demonstrated that, over a 2-10 year period, 36% progressed to diabetes (Ramachandran et al 1986).

The present study has demonstrated that, using WHO criteria, 50.4% of South African Indian subjects with IGT progressed to NIDDM over a 4 - year period, with a rate of progression of 12.6% per year - one of the highest recorded in the literature.

With respect to examination of risk factors associated with progression to NIDDM in subjects with IGT, a multitude of clinical and biochemical factors have been studied in the literature and include plasma glucose concentration at the initial (baseline) OGTT, age, sex, BMI, family history of diabetes, blood pressure, plasma insulin during OGTT, plasma lipids, serum creatinine.

Of all the factors studied to date, the single most important predictor (risk factor)for the subsequent progression to NIDDM in IGT subjects has been the *plasma glucose concentration* at the initial OGTT (O'Sullivan and Mahan 1968, Jarrett et al 1979, Keen et al 1982, Sazaki et al 1982, King et al 1984, Kadowaki et al 1984, Saad et al 1988, Schrantz AG 1989); other less consistent factors include *BMI* (Keen et al 1982, Jarrett et al 1984, Kadowaki et al 1984, Schrantz AG 1989) *age* (Saad et al 1988, Schrantz AG 1989) and *plasma insulin levels* (Kadowaki et al 1984, Sicree et al 1987, Saad et al 1988).

In the present study, when baseline variables at Year 0 were examined (Table 2 and 3), the significant independent predictive risk factors for subsequent progression to diabetes in IGT subjects included both **FASTING AND 2HR PLASMA GLUCOSE LEVELS;** sex and BMI which were significant in the univariate analysis, failed to achieve significance in the multivariate analysis.

That plasma glucose concentration at the baseline examination is the most significant independent predictor for the subsequent progression to diabetes has been demonstrated in all the reported prospective population based studies on subjects with IGT i.e. the higher the fasting plasma glucose level and/or the higher the level after a glucose load at baseline, the higher the risk for NIDDM (vide infra).

The finding in the present study that both fasting and 2hr plasma glucose levels are the most significant risk factors (predictors) is in accordance with the majority of the studies reported [O'Sullivan and Mahan 1968 (USA - whites); Birmingham Diabetes Survey Working Party 1970, 1976, (UK); Jarrett et al 1979 (UK - Whitehall); Sazaki et al 1982 (Japan); Kadowaki et al 1984 (Japan); King et al 1984 (Nauru - Micronesian); Saad et al 1988 (USA - Pima Indians); Schrantz AG 1989 (Malta)].

In three reported studies, only the 2hr plasma glucose level was found to be a significant predictor [Keen et al 1982 (UK-Bedford); Jarrett et al 1984 (UK - Whitehall); Knowler et al 1986 (US - Pima Indians)] - in the Bedford survey and Whitehall survey only 2hr plasma glucose values were included in the analysis, whilst in Pima Indian study, both fasting and 2hr plasma glucose values were examined. The finding of baseline fasting plasma glucose level as a predictor was reported in a study which examined the effect of diet and chlorpropamide on IGT subjects over a six year period [Stowers et al 1981 - (UK - Aberdeen)].

Therefore each of the studies quoted, including the presentstudy have observed different population groups, some selected in different ways and differing in the methods and criteria adopted for defining progression to diabetes - nevertheless, the single point that emerges is that the **BASELINE LEVELS OF BLOOD GLUCOSE** themselves, however defined, best predict subsequent progression to diabetes mellitus in IGT subjects.

The role of BMI (and obesity) as predictive risk factors for progression to diabetes in IGT subjects is less consistent. Obesity has sometimes [O'Sullivan and Mahan 1968, Keen et al 1982 (Bedford), Kadowaki et al 1984, Schranz AG 1989] though not invariably [Jarrett et al 1979 (Whitehall), Keen et al 1982 (Bedford), Sazaki et al 1982, King et al 1984, Saad et al 1988] been a significant predictor for subsequent development of diabetes.

In the present study, the mean BMI (p0.0019) and the prevalence of obesity (51.8% vs 28.6%, p0.012) was significantly higher in subjects who progressed to NIDDM compared to those who did not. However, BMI which was significant in the univariate analysis failed to achieve significance in the multivariate analysis - this finding is consistent with reported studies on other populations viz. Pima Indians (Saad et al 1988), Nauruans (King et al 1984), Japanese (Sazaki et al 1982). In the Bedford Survey (Keen et al 1982), BMI was not a significant predictive marker in the 1st five years, but achieved significance in the 2nd five years of the study period. In the Whitehall Study (Jarrett et al 1979), BMI was not significant even in the univariate analysis.

However, the role of BMI (and obesity) should not be completely dismissed, since it is possible that if the subjects were followed up for longer periods its significance may assume greater importance.

In the present study, univariate analsysis, showed that of the females 59.6% progressed to diabetes whilst 40.4% did not progress; the reverse was true for males in whom 41% progressed to NIDDM whilst 59%

did not - this appeared to indicate that the risk for subsequent development of NIDDM was higher in IGT females than males. However, sex, which was significant in the univariate analysis failed to achieve significance in the multivariate analysis - whether this was due to the confounding effect of obesity which was more prevalent in females, is not clear; but perhaps the close relationship between obesity and female sex could explain this finding.

In the present study, a positive family history of diabetes was not a predictor of subsequent progression to NIDDM in IGT subjects. This finding is consistent with other studies in which family history was examined as a risk factor [Saad et al 1988, Keen et al 1982 (Bedford), Jarrett et al 1979, 1984 (Whitehall), Kadowaki et al 1984, Schrantz AG 1989, King et al 1984].

An interesting finding in the present study was the trend in the proportion of study (IGT) subjects progressing to diabetes across quartiles and quintiles of blood glucose concentration (Table 8,9 Fig 1,2). In accordance with the other studies which have examined this aspect, the rate of deterioration to NIDDM in IGT subjects increased with increasing baseline plasma glucose concentration, both fasting and 2hr levels (Kadowaki et al 1984, King et al 1984, Saad et al 1988).

Of note, though, was that in the present study when different cut-off levels for baseline 2hr plasma glucose were examined, 100% (all) of the subjects who had 2hr plasma glucose ≥ 10.2 mmol/L at Year 0 (baseline) progressed to diabetes by the end of the study period, whilst none (0%) of the subjects with 2hr plasma glucose < 7.9 mmol/L at Year 0 progressed to NIDDM. In the Nauruan Study (King et al 1984), mean 2hr plasma glucose results in the group which progressed to diabetes and in the group which did not progress, were surprisingly similar to those found in the present study (ie. 9.5 vs 8.6 mmol/L in the Nauruans Study; 9.4 vs 8.6 mmol/L in the present study) - in the Nauruan Study, just over 50% of subjects in the highest quartile of 2hr plasma glucose (9.5 - < 11.1 mmol/L) subsequently progressed to diabetes, whereas in the present study, 78.9% in the highest quartile (9.4 - < 11.1 mmol/L) progressed to diabetes. However, unlike the present study, there appear to be no reports of actual cut-off levels above which all subjects with IGT become diabetic.

As regards fasting plasma glucose, the present study has demonstrated that all (100%) those subjects with fasting plasma glucose ≥ 7.3 mmol/L at baseline (Year 0), progressed to diabetes over the study period.

Therefore, from the results of the present study it would appear that in South African Indian subjects with IGT, the risk of progression to diabetes is total, if baseline 2hr plasma glucose is ≥ 10.2 mmol/L or if baseline fasting plasma glucose ≥ 7.3 mmol/L.

As discussed earlier, for the purpose of the present thesis, a separate analysis of data with Year 1 as baseline was undertaken, since more detailed clinical and biochemical parameters were examined.

When Year 1 was used as the baseline, the single independent predictive risk factor for subsequent progression to diabetes was **90 MIN PLASMA GLUCOSE LEVEL (MID-TEST LEVEL)**; systolic blood pressure, 30 min plasma glucose and 60 min plasma glucose and a positive history of paternal diabetes, which were significant in the univariate analysis failed to achieve significance in the multivariate analysis. None of the remaining numerous variables analysed were found to be significant viz. plasma insulin response during OGTT, insulin ratios, lipid levels, glycated haemoglobin, serum uric acid (Table 4 and 5), as well as fasting and 2hr-plasma glucose.

An interesting finding in the present study was that in the univariate analysis, systolic blood pressure was significantly higher in subjects who progressed to NIDDM although it lost significance in the multivariate analysis. Blood pressure has been analysed in four other reported studies [Saad et al 1988, King et al 1984, Jarret et al 1979, 1984 (Whitehall), Keen et al 1982 (Bedford)]. In the Bedford Survey and the 5-year report on the Whitehall Study (1979), blood pressure was not found to be significantly different in the group which progressed to NIDDM compared to the group which did not. In both the Nauruan and the 10 year report on the Whitehall Study (1984), systolic blood pressure, which was not significant in univariate analysis was found to be negatively associated with subsequent diabetes in the multivariate analysis; in the Nauruan Study this finding was explained by the confounding effect of age but in the Whitehall Study the finding was difficult to explain.

This is at variance with the report on Pima Indians (Saad et al 1988) in which, those IGT subjects who progressed to NIDDM were characterised by higher baseline fasting insulin, lower post load (2hr) insulin, lower post load insulin : glucose ratio and lower post load ratio of increment of insulin to increment of glucose. The finding of decreased post load insulin as a predictor for subsequent diabetes has been reported in two other studies (Kadowaki et al 1984, Sicree et al 1987). In the Japanese Study, decreased 30 min insulin level was significant whilst in Nauruans, ↓ ed 2hr insulin level was found to be a significant predictor. Of note, though, was that in the Nauruan Study, a diminished 2hr insulin response just failed to achieve significance in the multivariate analysis, and that it only achieved significance with the use of the glucose-insulin interaction term.

Saad's finding that decreased insulin response served as a predictor for diabetes in Pima Indians was confirmed in another study (Knowler WC and Bennett PH 1983); however in a third and earlier study on Pima Indians, no evidence was found that subjects destined to have diabetes had either excessive or diminished insulin response (Savage et al 1975). In the Bedford Study (Keen et al 1982), 2hr plasma insulin was analysed but was not found to be a predictor.

The obvious limitation in the present study is the lack of adequate data on insulin response at Year 0 (due to an unforeseen laboratory disaster).

The finding in the present study that when Year 1 was used as baseline, the significant predictor was 90 min plasma glucose (mid-test level) deserves comment.

As discussed in Chapter 5 and alluded to above, some of the prospective studies on IGT were undertaken prior to the introduction of the currently employed WHO criteria for glucose tolerance viz. in American Whites (O'Sullivan and Mahan 1968), British males (Birmingham Diabetes Survey Working Party 1970, 1976), Japanese subjects (Sazaki et al 1982, Kadowaki et al 1984), Swedes (Sartor et al 1980), Bedford (Keen et al 1982), Whitehall Survey (Jarrett et al 1979). Notwithstanding their value with respect to the understanding of the category of IGT_1, they differed from the present one either because different criteria for glucose tolerance were employed (O'Sullivan and Mahan 1968, Birmingham Survey 1970, 1976, Jarrett et al 1979, Keen et al 1982, Sartor et al 1980, Kadowaki et al 1984), different glucose loads were employed (all the studies quoted above), OGTT's were performed in the afternoon (Jarrett et al 1979, 1984) or because subjects were clinic based (Kadowaki et al 1984, Ramachandran et al 1986).

Prospective studies employing WHO criteria (75G OGTT after overnight fast) include those on Nauruans (King et al 1984), Pima Indians (Saad et al 1988, Knowler et al 1986), and Maltese (Schrantz AG 1989) - in all these studies which were large scale epidemiological studies, only fasting and 2hr plasma glucose levels were estimated (as recommended by WHO), as was the case in the baseline examination (Year 0) of the present study; mid-test glucose levels were not estimated.

Currently, the most widely employed criteria for glucose tolerance include those of the WHO (1980, 1985) and the NDDG (1979). As discussed in the Chapter on WHO vs NDDG criteria, whilst the recommendations of the two groups were similar in many ways, two major differences between them include (a) cut off levels for fasting plasma glucose and (b) the requirement for mid-test samples in the NDDG recommendation as opposed to only fasting and 2hr samples recommended by WHO.

Subsequent to its original recommendation (1979), the NDDG reviewed the international criteria for the diagnosis of diabetes and IGT (Harris et al 1985); from that review it was concluded that the WHO system represented a simpler, inclusive classification scheme and that there was insufficient evidence from longitudinal studies of any prognostic difference that would justify the more complicated NDDG diagnostic criteria (which included mid-test samples). Another reason why mid-test values were not considered essential was that whilst there were studies which confirmed fasting and 2hr plasma glucose values as predictive risk factors for the development of diabetes in IGT subjects, there was no data to support such findings for any particular mid-test value.

One of the reasons for the appeal from the WHO (1980, 1985) for population-based studies on IGT_1 is that such studies might provide evidence concerning the present diagnostic criteria for glucose tolerance.

In the present study, at Year 0, fasting and 2hr plasma glucose levels were estimated (in accordance with WHO recommendations). Those subjects examined at Year 1, 2 and 4 had OGTT with mid-test plasma glucose estimations as well (0, 15, 30, 60, 90 and 120 min). At Year 1, 47 subjects were diagnosed as IGT (IGT_1). In order to assess the significance of the numerous biochemical parameters examined, Year 1 was used as baseline for the follow up of IGT_1 subjects.

An interesting finding in the present study was that when Year 1 was used as baseline, the most siginficant predictive risk factor for subsequent progression to diabetes was the 90-min plasma glucose (mid-test level); a surprising finding was that neither fasting nor 2hr plasma glucose were significant.

Comparison with other studies is not possible, since none of the quoted prospective studies have examined mid-test glucose levels, and there exists therefore, no data indicating whether a particular mid-test glucose value is a better predictor than fasting and 2hr glucose values.

In the more recent evaluation of WHO and NDDG criteria for IGT (Modan et al 1989), it has been suggested that in prospective studies of IGT, at least 3 plasma glucose samples during OGTT viz. fasting + 2hr + mid-test (30, 60, or 90 min) be used. The finding of the present study would support this view; however, whether subjects should have 3 mid-test values (30, 60 and 0 min) or only a single mid-test values (and if so, which mid-test value) is not clear, especially in view of the finding in the present study that the 90 min and not 60 min value was a significant predictor; moreover there still exists the practical problem of multiple venepunctures in large scale epidemiological studies.

Certainly, the finding in the present study emphasises the need for further studies to assess the significance of mid-test glucose values in subjects with IGT.

In summary, the present study on the evaluation of risk factors associated with progression to diabetes mellitus in the study group, has demonstrated that :

1) When Year 0 was used as baseline, the significant predictive risk factors were fasting and 2hr plasma glucose concentration.
2) When Year 1 was used as baseline, the significant predictor was 90 min glucose concentration (mid-test value).

Therefore, in conclusion, the present study which has examined the factors associated with the high rate of progression to diabetes mellitus in South African Indian subjects with IGT, has demonstrated findings which support those of previously reported studies - that, of all the factors studied, the single most important predictor of subsequent diabetes subjects with IGT is the baseline plasma glucose concentration.

SUMMARY

In this 1-4 year (Year 1 - Year 4) prospective study of the natural history of IGT in 128 South African Indians who were diagnosed as IGT at Year 0 of the study (IGT_0), 113 subjects satisfactorily completed the study, either by returning for follow-up OGTT, or because they had reached the end point of the study i.e. the date of diagnosis of NIDDM. Over the study period, 57 (50.4%) of the 113 IGT_0 subjects progressed to diabetes mellitus, 28 (24.8%) persisted with IGT and 28 (24.8%) recerted to Normal Glucose Tolerance. At Year 1, 47 subjects were diagnosed as (IGT_1), of whom 40 subjects satisfactorily completed the study.

In those subjects who satisfactorily completed the study, examination for risk factors predictive of subsequent progression to diabetes was undertaken by analyses of baseline clinical and biochemical variables; this was performed in two ways: using Year 0 as baseline for the 113 IGT_0 subjects, and (for the purpose of the thesis) using Year 1 as the baseline for the 40 IGT_1 subjects.

When Year 0 was used as baseline, of the six factors examined, the significant predictive risk factors for subsequent progression to diabetes were the fasting and 2hr plasma glucose concentration. Using cut-off levels for baseline plasma glucose concentration, it was demonstrated that all subjects who at Year 0, had 2hr plasma glucose $\geq$ 10.2 mmol/L or fasting plasma glucose $\geq$ 7.3 - $<$ 7.8 mmol/L, subsequently progressed to diabetes.

When Year 1 was used as baseline, of the 28 variables analysed, only the 90 min plasma glucose concentration (mid-test level) was predictive of progression to diabetes.

Therefore, in South African Indians, IGT is associated with a high risk for progression to diabetes, and in this group the most significant predictor of subsequent diabetes is the baseline plasma glucose concentration.

CHAPTER 14

WHO vs NDDG CRITERIA

INTRODUCTION

Currently, the most widely used criteria for the diagnosis of diabetes and other categories of glucose tolerance, are based on the WHO Expert Committee on diabetes and the National Diabetes Data Group (WHO 1980, 1985, NDDG 1979). Table 1 and 2. Both groups have published recommendations regarding methodology and criteria for the diagnosis of diabetes mellitus, IGT and Normal glucose tolerance in non-pregnant subjects.

The recommendations promulgated by the two groups are similar in several ways:

1) Both permit the diagnosis of diabetes in asymptomatic individuals with unequivocally elevated plasma glucose concentrations.
2) Both recommend that in asymptomatic individuals, a 2-hr 75G OGTT be performed to establish a diagnosis of diabetes or IGT.

However, there are 2 major differences between the two sets of diagnostic criteria (Table 3) that lead to discrepancies in classification of individuals based on OGTT results:

1) To class an OGTT as Normal, NDDG requires a FBG <6.4mmol/L, whereas WHO, whilst not stipulating an upper limit of normal, implies that FBG may not ≥7.8mmol/L, since such levels constitute diabetes.

2) NDDG recommends 5 plasma glucose values, whereas WHO requires only 2. Both require fasting and 2-hr post load glucose values, but NDDG also recommends that glucose values at ½ hr, 1 hr or 1½ hr post load (mid-test levels) be used in order to determine an individuals's diagnostic class. If the glucose level of one of these mid-test samples does not meet certain specific criteria, the OGTT is considered "NON-DIAGNOSTIC" in the NDDG classification. To classify an individual using WHO criteria, mid-test glucose values are not considered, and need not be obtained.

It is the "non-diagnostic" OGTT that causes the greatest discrepancy between the 2 sets of criteria (Harris et al 1985).

Subsequent to the original recommendations of the NDDG, several workers undertook analysis of large numbers of OGTT using both WHO and NDDG criteria, and highlighted the discrepancy caused by the inclusion of the "non-diagnostic" OGTT (Massari et al 1983, Modan et al 1984). The NDDG itself reviewed the international criteria for the diagnosis of diabetes and IGT (Harris et al 1985), employing both WHO and NDDG criteria; the findings in that study supported those of the previously quoted reports; and conclusions were made as to which of the 2 sets of criteria (WHO or NDDG) was to be recommended for future use.

Table 1

DIAGNOSTIC VALUES FOR ORAL GLUCOSE TOLERANCE TEST UNDER STANDARD CONDITIONS. LOAD 75g GLUCOSE IN 250-350ml OF WATER FOR ADULTS OR 1.75g/Kg BODY WEIGHT (TO A MAXIMUM of 75g) FOR CHILDREN, USING SPECIFIC ENZYMATIC GLUCOSE ASSAY.

	GLUCOSE CONCENTRATION mmol/litre (mg/dl)			
	WHOLE BLOOD		PLASMA	
	Venous	Capillary	Venous	Capillary
Diabetes Mellitus				
Fasting Value				
	≥6.7	≥6.7	≥7.8	≥7.8
	(≥120)	(≥120)	(≥140)	(≥140)
2 Hours After Glucose Load				
	≥10.0	≥11.1	≥11.1	≥12.2
	(≥180)	(≥200)	(≥200)	(≥200)
Impaired Glucose Tolerance				
Fasting Value				
	<6.7	<6.7	<7.8	<7.8
	(<120)	(<120)	(<140)	(<140)
2 Hours After Glucose Load				
	6.7-10.0	7.8-11.1	7.8-11.1	8.9-12.2
	(120-180)	(140-200)	(140-200)	(160-220)

Table 2

DIABETES MELLITUS IN NONPREGNANT ADULTS

Any one of the following are considered diagnostic of diabetes:

A. Presence of the classic symptoms of diabetes, such as polyuria, polydipsia, ketonuria, and rapid weight loss, together with gross and unequivocal elevation of plasma glucose.

B. Elevated fasting glucose concentration on more than one occasion.

venous plasma ≥ 140 mg/dl (7.8 mmol/L)
venous whole blood ≥ 120 mg/dl (6.7 mmol/L)
capillary whole blood ≥ 120 mg/dl (6.7 mmol/L)

If the fasting glucose concentration meets these criteria, the OGTT is not required. Indeed, virtually all persons with FPG > 140 mg/dl will exhibit an OGTT that meets or exceeds the criteria in C below.

C. Fasting glucose concentration less than that which is diagnostic of diabetes (B, above), but sustained elevated glucose concentration during the OGTT on more than one occasion. Both the 2-h sample and some other sample taken between administration of the 75-g glucose dose and 2-h later must meet the following criteria:

venous plasma ≥ 200 mg/dl (11.1 mmol/L)
venous whole blood ≥ 180 mg/dl (10.0 mmol/L)
capillary whole blood ≥ 200 mg/dl (11.1 mmol/L)

IMPAIRED GLUCOSE TOLERANCE (IGT) IN NONPREGNANT ADULTS

Three criteria must be met: the fasting glucose concentration must be below the value that is diagnostic for diabetes; the glucose concentration two hours after a 75-G oral glucose challenge must be between normal and diabetic values; and a value between ½-h, 1-h or 1½-h OGTT value later must be unequivocally elevated.
Fasting value:

venous plasma < 140 mg/dl/L (7.8 mmol/L)
venous whole blood < 120 mg/dl/L (6.7 mmol/L)
capillary whole blood < 120 mg/dl/L (6.7 mmol/L)

½-h, 1-h, or 1½-h OGTT value:

venous plasma ≥ 200mg/dl (11.1 mmol/L)
venous whole blood ≥ 180 mg/dl/L (10.ommol/L)
capillary whole blood ≥ 200 mg/dl (11.1 mmol/L)

2-h OGTT value:

venous plasma of between 140 and 200 mg/dl (7.8 and 11.1 mmol/L)
venous whole blood of between 120 and 180 mg/dl (6.7 and 10.0 mmol/L)
capillary whole blood of between 140 and 200 mg/dl (7.8 and 11.1 mmol/L)

NORMAL GLUCOSE LEVELS IN NONPREGNANT ADULTS

Fasting value:

venous plasma < 115 mg/dl (6.4 mmol/L)
venous whole blood < 100 mg/dl (5.6 mmol/L)
capillary whole blood < 100 mg/dl (100mmol/L)

2-h OGTT value:

venous plasma < 140 mg/dl (7.8 mmol/L)
venous whole blood < 120 mg/dl (5.6 mmol/L)
capillary whole blood < 140 mg/dl (7.8 mmol/L)

OGTT values between ½-h, 1-h, or 1½-h OGTT value later:

venous plasma < 200 mg/dl (11.1 mmol/L)
venous whole blood < 180 mg/dl (10.0 mmol/L)
capillary whole blood < 200mg (11.1 mmol/L)

Glucose values above these concentrations but below the criteria for diabetes or IGT should be considered nondiagnostic for these conditions.

Table 3

NDDG AND WHO CRITERIA

	Plasma glucose mg/dl (mmol/L)*				
			ORAL GLUCOSE TOLERANCE TEST		
CLASS	FASTING		MIDTEST		2-HR
NDDG					
Normal	<115(<6.4)	and	<200(<11.1)	and	<140(<7.8)
IGT	<140(<7.8)	and	≥200(≥11.1)	and	140-199(7.8-11.1)
Diabetes[+]	≥140(≥7.8)	or	≥200(≥11.1)	and	≥200(≥11.1)
Non diagnostic	all other combinations of fasting, midtest, and 2-hr values				
WHO					
Normal[++]	<140(<7.8)		-	and	<140(<7.8)
IGT	<140(<7.8)		-	and	140-199(7.8-11.1)
Diabetes[+]	≥140(≥7.8)		-	or	≥200(≥11.1)

* The mmol/L values were computed by dividing mg/dl by 18.016 (the number of milligrams of glucose in 1 dl of a 1mM solution) and rounding to the nearest 0.1 mmol/L WHO obtained mmol/L values by dividing mg/dl values by 18 and rounding to the nearest 1 mmol/L.

[+] NDDG and WHO require both the fasting and 2-hr values to classify a subject, except when the fasting is ≥140mg/dl, which by itself is diagnostic of diabetes.

[++] Although WHO does not define a "normal" OGTT, the term is used here to include subjects who do not meet criteria for diabetes or IGT.

This chapter evaluates the WHO and NDDG criteria in the 128 study subjects, who were originally diagnosed as IGT based on WHO criteria.

METHODS

Background:

The present study was undertaken to examine prospectively IGT in South African Indians, based on WHO criteria (Table 1,4).

At Year 1, a 75-G OGTT was performed on all the 128 study subjects who were classified as IGT a year previously (Year 0) (as described in Chapter 2, 4 & 5).

Based on WHO criteria, the study subjects were classified into 3 categories of glucose tolerance at Year 1 viz IGT_1 (47 subjects), $Diabetes_1$ (41 subjects) and $Normal_1$ (40 subjects).

Further follow-up was determined according to the category to which the subjects belonged: (i) the end point of study for any subject was the date of diagnosis of NIDDM (ii) all those subjects who were IGT_1 or $Normal_1$ were requested to undergo an OGTT at Year 4 (iii) in addition, a subset of the IGT_1 and $Normal_1$ group had follow-up OGTT at Year 2; again the end point of study for any subject was the development of NIDDM.

Methods:

1) The results of the OGTT at Year 1 were classified on the basis of both the WHO (Table 1) and NDDG (Table 2) criteria.
Since in the present study, mid test values were not obtained at Year 0 (which was an epidemiology survey), comparison between WHO and NDDG criteria was considered more meaningful for the OGTT's done at Year 1, 2 and 4.

2) With respect to the subset which was examined at Year 2, only the results of the OGTT of the 7 subjects who developed Diabetes were examined; in the remaining subjects, only the results of the OGTT done at Year 4 were analysed (since all these subjects had OGTT done both at Year 2 and 4).

3) Since the end-point in this study was the diagnosis of NIDDM, an analysis of the initial diagnostic category (WHO or NDDG) was undertaken, to determine which set of criteria was more predictive of the development of diabetes.

4) A closer examination was undertaken of the fate of the "non-diagnostic" OGTT category.

RESULTS

Results summarised in Table 4,5,6 ; Figure 1 and 2.

OGTT at Year 1 Table 4 and 5

Of the 128 OGTT done at Year 1, using WHO criteria, 36.7% (47 subjects) were classified IGT, 32% (41 subjects) Diabetes and 31.3% (41 subjects) Normal.

When NDDG criteria were employed, 21.9% (28 subjects) were classified IGT, 32% (41 subjects) Diabetes, 23.4% (30 subjects) Normal and 22.7% (29 subjects) "non-diagnostic". Thus NDDG and WHO agreed in classification of 77.3% of OGTT's.

Of the 128 subjects studied at Year 1, the proportion which was diagnosed as Diabetes (32%, 41 subjects) was identical, whether WHO or NDDG criteria were employed.

The discrepancy between the systems arose with the finding that 22.7% (29 subjects) had "non-diagnostic" OGTT based on NDDG criteria; this resulted in a lower prevalence of Normal, and particularly IGT class i.e. the NDDG systems could not place more than one in five OGTT's (22.7%) in a diagnostic class (Normal, IGT or Diabetes).

Of the 47 subjects classified IGT by WHO, only 28 were classified IGT using NDDG criteria i.e. 40% (19 subjects) were designated

Table 4

CLASSIFICATION BASED ON CRITERIA FOR GLUCOSE TOLERANCE (WHO, NDDG): STUDY GROUP AT YEAR 1

DIAGNOSTIC CRITERIA (number examined)	CATEGORY OF GLUCOSE TOLERANCE			
	DIABETES %(n)	IGT %(n)	NORMAL %(n)	NON-DIAGNOSTIC %(n)
WHO (128)	32.0 (41)	36.7 (47)	31.3 (40)	
NDDG (128)	32.0 (41)	21.9 (28)	23.4 (30)	22.7 (29)

"non-diagnostic" according to the NDDG system.

Follow-up of subjects with "non-diagnostic" OGTT at Year 1. Figure 1.

By Year 4, of the 29 subjects with "non-diagnostic" OGTT at Year 1:

3 (10.3%) *progressed* to Diabetes

5 (17.2%) *progressed* to IGT

4 (13.8%) *reverted* to Normal

14 (48.3%) *persisted* as "non-diagnostic"

and 3 (10.3%) - no follow-up

Therefore 27.5% developed abnormal glucose tolerance by Year 4, using NDDG criteria.

Follow-up of subjects with IGT (WHO) but "non-diagnostic" OGTT using NDDG criteria: Figure 2.

By Year 4, of the 19 IGT_1 subjects (WHO), classified "non-diagnostic" (NDDG):

3 (15.8%) *progressed* to Diabetes

3 (15.8%) *progressed* to IGT

2 (10.5%) *reverted* to Normal

10 (52.6%) *persisted* as "non-diagnostic"

1 (5.3%) - no follow up

Therefore 31.6% developed abnormal glucose tolerance by Year 4, using NDDG criteria.

FIGURE 1

FOLLOW-UP OF 29 SUBJECTS WITH "NON-DIAGNOSTIC" OGTT AT YEAR 1

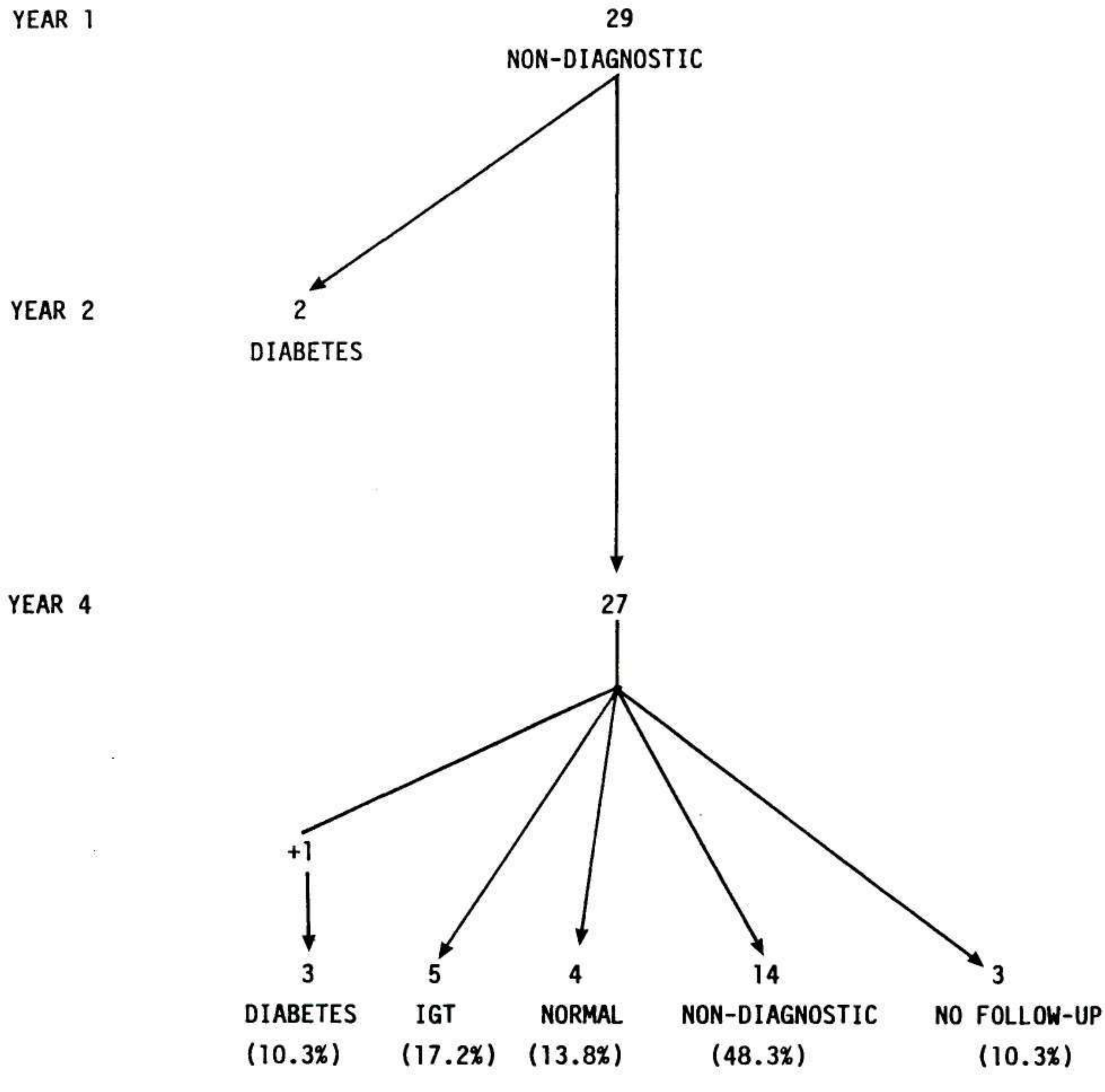


FIGURE 2

FOLLOW-UP OF 19 IGT1 (WHO) SUBJECTS CLASSIFIED "NON-DIAGNOSTIC" BY NDDG

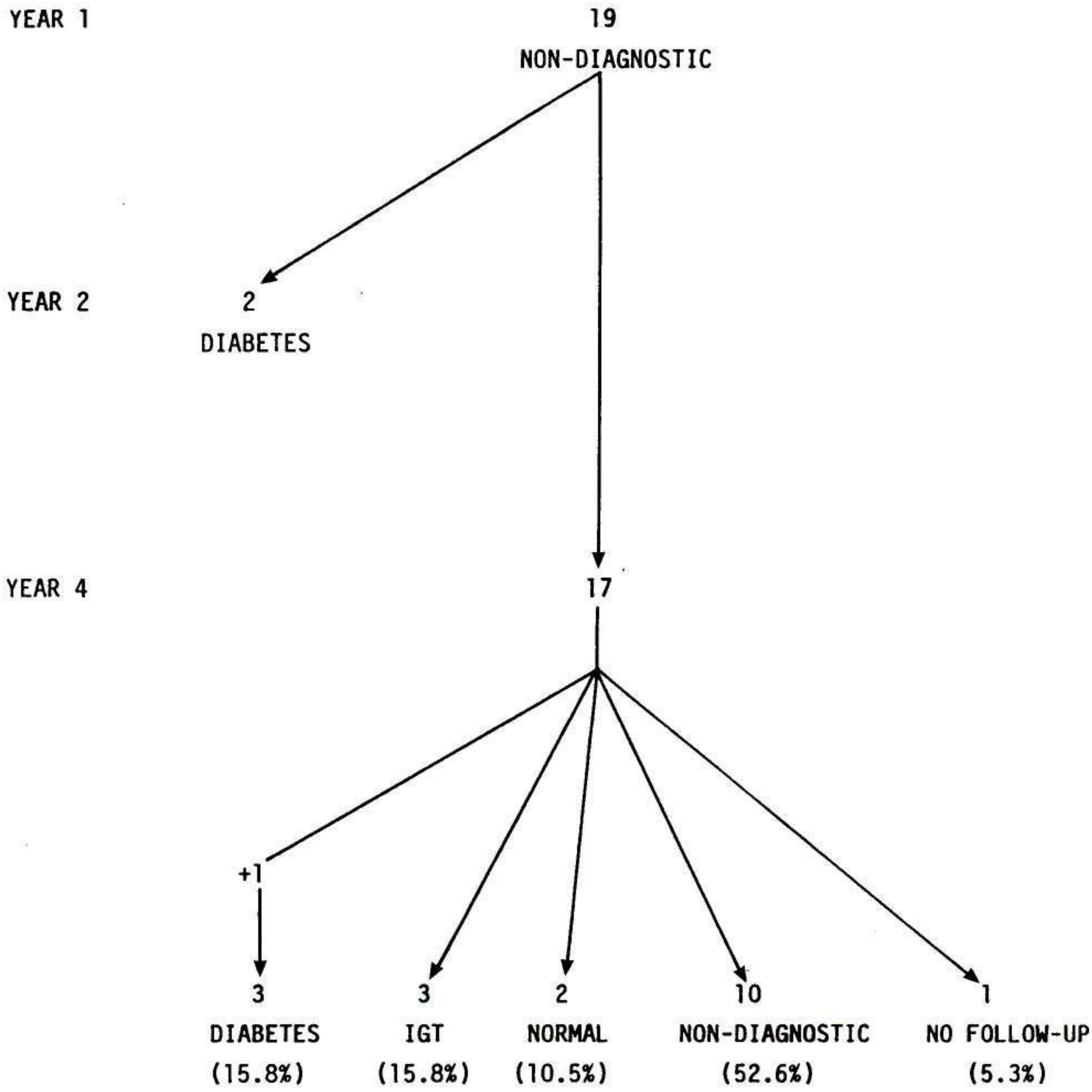


TABLE 5

FOLLOW-UP CLASSIFICATION OF 47 SUBJECTS DIAGNOSED IGT AT YEAR 1
BASED ON WHO CRITERIA : WHO vs NDDG CRITERIA

WHO class (number)	NDDG Class						
	YEAR 1			Year 2 or 4			
	IGT n(%)	*Non-diag n(%)	Normal n(%)	IGT n(%)	*Non diag n(%)	Normal n(%)	Diabetes n(%)
YEAR 1							
IGT_1 (47)	28(59.6)	19(40.4)					
FOLLOW-UP:							
(a) YEAR 2							
$Diabetes_2$ (7)	5(71.4)	2(28 6)					7(100)
(b) YEAR 4							
IGT_4 (17)	5(29.4)	12(70.6)		8(47.1)	9(52.9)		
$Normal_4$ (7)	4(57.1)	3(42.9)			3(42.9)	4(57.1)	
$Diabetes_4$ (9)	8(88.9)	1(11.1)					9(100)
(c) NO FOLLOW-UP							
IGT_1 (7)	6(85.7)	1(14.3)					
TOTAL				8 +	12 +	4	+ 16
					= 40		

*Non-diagnostic

Classification at Year 1, of subjects who developed Diabetes by Year 4

Table 6.

Using WHO criteria, all 16 subjects who progressed to Diabetes by Year 4, were classified IGT at Year 1.

However, when NDDG criteria were employed, only 81.3% (13 subjects) who progressed to Diabetes by Year 4, were Classified IGT at Year 1.

Table 6

INITIAL CLASSIFICATION OF 16 SUBJECTS DIAGNOSED DIABETES BY YEAR 4

CLASSIFICATION BY Year 4 - n (WHO/NDDG)	CLASSIFICATION AT YEAR 1	
	WHO class - n (%)	NDDG class - n (%)
Diabetes 16	IGT 16(100%)	IGT 13(81.3%) Non-diag 3(18.7%)

DISCUSSION

The introduction of the category of Impaired Glucose Tolerance (IGT) by the National Diabetes Data Group (1979) and its subsequent adoption by the World Health Organisation (WHO) Expert Committee on Diabetes (1980, 1985), was based on the observation that there are a substantial number of individuals who have fasting plasma glucose concentration lower than that required for the diagnosis of diabetes, but in whom the plasma glucose response during an oral glucose tolerance test (OGTT) is intermediate between normal and diabetic levels.

Several prospective studies on subjects classified as IGT, have highlighted an increased risk in such subjects, of subsequent development of diabetes mellitus and macrovascular disease (NDDG 1979).

Currently, the criteria most widely used for the classification of glucose tolerance based on a 75-G OGTT, are those of the WHO (1980, 1985) and NDDG (1979). However, whilst both groups include in their classification, a category of "IGT", the criteria for its diagnosis differ somewhat:

i) According to the WHO system, only 2 blood samples (fasting and 2 hr post load) are required; whilst the NDDG system requires mid-test samples (½hr, 1hr or 1½ post load) in addition i.e. the NDDG system demands stricter criteria for the diagnosis of IGT.

ii) When WHO criteria are employed, an OGTT will be classified as Normal, IGT or Diabetes; however, with NDDG criteria, an OGTT may be classified as Normal, IGT, Diabetes or "non-diagnostic", the latter causing the greatest discrepancy between the WHO and NDDG classifications.

Of note , was that both the WHO and NDDG highlighted the significance of IGT with respect to future risk of development of diabetes and macrovascular disease. However, in its original recommendations for classification of glucose tolerance (NDDG 1980), whilst NDDG included the "non-diagnostic" OGTT, the significance of this category was not established and no recommendations were made as to whether subjects with "non-diagnostic" OGTT needed to be followed up.

In a French study, an analysis of OGTT's employing different sets of criteria was undertaken in 543 subjects attending a Paris diabetes screening clinic. It was demonstrated in that study that, when NDDG criteria were employed, 33% of their study group were excluded from the three clinical classes (Normal, IGT, Diabetes); of these 2/3 corresponded to the "non-diagnostic" category and 1/3 were "unclassifiable"; moreover, the prevalence of Diabetes and IGT were 10% and 41% lower, respectively, using NDDG rather than WHO criteria (Massari et al 1983).

In a study of over 2000 Israeli Jewish subjects, the prevalence of diabetes was 5% lower and that of IGT 63% lower with the use of NDDG criteria (Modan et al 1984) when compared to WHO criteria.

Subsequent to its original recommendations (1979), the NDDG reviewed the international criteria for the diagnosis of diabetes and Impaired Glucose Tolerance (Harris et al 1985). Both WHO and NDDG criteria were employed in an analysis of over 3000 OGGT's performed in a prevalence survey in the United States. The results of that study demonstrated that for 87.7% of the OGGT's, the two systems agreed in classification. For the remainder, they differed, primarily because "non-diagnostic" OGTT occured with NDDG criteria, but not with those of WHO; the major discrepancy occured with IGT classification - the prevalence of IGT was more than twice using WHO criteria (11.6%) compared to NDDG criteria (4.9%); the prevalence rates of Diabetic OGTT's were similar with both sets of criteria; the NDDG system could not place one in eight OGTT (12.3%) into a diagnostic category. It was concluded that the WHO system respresented a simpler, inclusive classification scheme, and that there was insufficient evidence from longitudinal studies of prognostic difference that would justify the more complicated NDDG diagnostic criteria; moreover, it was concluded that in situations where multiple venous puncture or retesting were not possible, that glucose levels 2 hrs after 75G oral glucose load appeared to be the most appropriate single value to designate whether an individual has Diabetes, IGT or neither, since it identified 97% of all subjects in the same class as when full WHO criteria were employed. Another reason why mid-test values were not considered essential was that whilst there were studies which confirmed the fasting and 2hr glucose values as significant predictive risk factors for the development of diabetes in IGT subjects, there was no data to support such findings for any particular mid-test value.

The point was also made though, that whilst WHO criteria were recommended, it remained to be determined (from longitudinal studies) whether the WHO or NDDG criteria were more predictive of diabetic complications, and (relevant to the present study) if the respective criteria for IGT are predictive of the development of diabetes per se.

Whilst there have been published reports of cross-sectional studies which include mid-test values during OGTT, to date, most of the reports on prospective studies on IGT have examined only fasting and 2hr post load glucose values. The present study offers the advantage in that at Year 1, 2 and 4, mid-test values (½hr, 1hr, 1½hr) were obtained during OGTT, and hence makes comparison between WHO and NDDG systems more meaningful.

The finding in the present study, that the number of OGTT's classified as Diabetes was identical (41 at Year 1, 7 at Year 2, 9 at Year 4), irrespective of whether the WHO or NDDG criteria were employed, is better than that found in the study by Harris et al (1985); the likely reason is that 3 mid-test values were obtained in the present study, as opposed to only a single (1hr) mid-test value obtained in the study quoted.

As with the three studies quoted above, the present study demonstrated that the major discrepancy between the WHO and NDDG criteria arose with the "non-diagnostic" OGTT of the NDDG system; at Year 1, a significant proportion (22.7%) of the 128 OGTT's were "non-diagnostic" i.e. more than one in five OGTT's could not be placed into a diagnostic category.

The "non-diagnostic" OGTT affected particularly the IGT class - thus at Year 1 the prevalence of IGT was 40% lower when NDDG criteria were employed (21.9%) rather than those of WHO (36.7%).

Whilst the "non-diagnostic" OGTT was proposed in the original NDDG classification (1979), the significance of this category was not established, and no recommendations were made as to whether such subjects needed to be followed up, as was the case for subjects classified as IGT. To date, there appear to be no published reports on the follow-up of subjects with "non-diagnostic" OGTT. An interesting finding in the present study, was that of the 29 subjects calssified "non-diagnostic" at Year 1, 27.5% developed abnormal glucose tolerance by Year 4; of the 19 subjects who were classified IGT by WHO, but "non-diagnostic" by NDDG criteria, 32% developed abnormal glucose tolerance. Thus, if NDDG criteria were still to be employed, it would be important to recognise that subjects with "non-diagnostic" OGTT are at risk of developing diabetes and should therefore require follow-up; however, this also serves to strengthen the argument for the use of WHO criteria which is able to place all OGTT's into a diagnostic class.

One of the points raised by the NDDG (Harris et al 1985) was that whilst WHO criteria were to be recommended, it remained to be seen whether the WHO or NDDG criteria for IGT are better predictive of the development of diabetes. In this regard, the present study has demonstrated that of the subjects who developed Diabetes by Year 4, 100% were classified IGT at Year 1, using WHO criteria; however only 81.3% were classified IGT with NDDG criteria; thus providing further evidence in support of WHO criteria.

Therefore, in conclusion , the results of the present study confirm that the WHO criteria for classification of glucose tolerance have an advantage over those of the NDDG, since it can classify all subjects by way of a simpler, inclusive scheme; requires only two blood samples; moreover, its criteria for IGT correctly identified all those subjects who were at risk of developing diabetes.

On the other hand, the NDDG requires five blood samples, employs a more complicated classification scheme which includes a large proportion of "non-diagnostic" OGTT (with a resultant lower prevalence of IGT and Normal); moreover, the NDDG criteria for IGT failed to identify 18.7% of those subjects who were at risk for subsequent development of diabetes.

SUMMARY

The WHO and NDDG criteria for glucose tolerance were applied to the OGTT's of the 128 study subjects at Year 1, 2 and 4.

At Year 1, the WHO and NDDG systems were in agreement as regands classification 77.3% of OGTT's. For the remainder, they differed, primarily because a large proportion (22.7%) were "non-diagnostic" OGTT, when NDDG but not WHO criteria were employed. The difference resulted in the prevalence of IGT using WHO criteria (37%) being almost twice that using NDDG criteria (21.9%). The proportion of OGTT's which were Diabetes at Year 1 (32%) was identical, whether NDDG or WHO criteria were used.

Of the 29 OGTT initially classified "non-diagnostic" at Year 1, 27.5% were classified as abnormal glucose tolerance by Year 4 (10.3% Diabetes, 17.2% IGT).

Using WHO criteria, all the OGTT which were Diabetes by Year 4, were classified IGT at Year 1; however, when NDDG criteria were employed, only 81.3% of OGTT's which were Diabetes by Year 4, were classified IGT at Year 1.

The WHO is a simpler, inclusive scheme of classification and its criteria for IGT identified all those subjects at risk for subsequent diabetes.

CHAPTER 15

SUMMARY AND CONCLUSION

This prospective study on South African Indians with IGT was prompted by an appeal from the WHO Expert Committee on Diabetes (1980, 1985) for population based studies on such subjects in the hope that it would bring to light any distinctive features that may have a bearing on the pathogenesis and natural history of IGT in this population.

The cross-sectional aspect of the study ie. Year 1, allowed for examination of the clinical and biochemical parameters, both for the study group as a whole (Total Study Group) as well as for the study group based on the category of glucose tolerance at Year 1 (IGT_1 $Diabetes_1$ $Normal_1$).

As regards the clinical features, this study has highlighted an association between IGT and the following parameters viz. age, BMI (and obesity) and blood pressure. The observation that 88.3% of the subjects were ≥ 35 years and that 93.8% ≥ 30 years, confirms that in South African Indians, IGT is associated with increased age, more so than in Pima Indians and Nauruans (Bennett 1971, King et al 1984). The study group exhibited a high mean BMI (25.8) and prevalence of obesity (42%), both of which were more pronounced in females. When compared to age, sex and BMI matched control subjects, the mean blood pressure and prevalence of hypertension (17.2%) were higher in the study group.

When the study group was divided according to the category of glucose tolerance at Year 1, it was demonstrated that age, BMI, blood pressure, prevalence of obesity and hypertension increased with increasing degree of glucose intolerance (ie. $Normal_1 \rightarrow IGT_1 \rightarrow Diabetes_1$).

An interesting finding in the present study was that a positive family history of diabetes was as high in the Control group (53.1%) as in the study group (53.9%). This probably reflects the high prevalence of diabetes mellitus in this population group.

The lack of evidence for microvascular complications viz diabetic retinopathy, in the present study supports the findings of most other workers (Bennett et al 1971, Jarett and Keen 1976, Zimmet et al 1984). However, it must be noted that this may not be a true reflection in view of the obvious limitations of the present study viz. examination of the undilated eye and the fact the urine examination for albuminuria was not undertaken.

Thus, from the clinical findings, it would appear that this group of individuals (ie. IGT subjects) already possesses characteristics associated with the risk of development of both diabetes mellitus as well as macrovascular disease viz. increased age, body mass index and blood pressure.

As regards analysis of investigative methods (biochemical, electrocardiographic, tests for genetic markers), the most significant findings were those with respect to insulin response and electrocardiogram findings; analysis of lipid levels proved less impressive; that of uric acid levels interesting, whilst examination of glycated haemoglobin and genetic markers proved on the whole unimportant.

Examination of the plasma insulin response during OGTT demonstrated that South African Indians with IGT are characterised by both hyperinsulinaemia (and therefore, insulin resistance) and relatively insufficient pancreatic B cell secretory capacity (secretory defect). When compared to the control group, the study subjects exhibited higher plasma insulin levels (hyperinsulinaemia), both fasting and 2hr post load levels, although only significantly so at 2hrs; displayed a pattern of insulin response during OGTT which was different ie. a more delayed response with maximum levels being achieved only at 120 min (2hr); displayed heterogeneity of plasma insulin response; and had lower Insulinogenic Index - this was true whether the study group was examined as a whole as well as when divided according to category of glucose tolerance at Year 1 (ie. IGT_1 group).

Therefore, the results of the present study lend support to the concept of post load hyperinsulinaemia (and therefore insulin resistance) in subjects with IGT, and confirms the findings of other workers (Savage et al 1975, Zimmet et al 1978, Martin et al 1980, Reaven G and Miller 1968, Reaven et al 1976, 1989, Reaven GM and Olefsky JM 1977). The finding that fasting insulin levels were not significantly higher, whilst in accordance with the aforementioned studies, is at variance with another report on Pima Indians, in which fasting levels were also significantly elevated (Lillioja et al 1988). That similar results were obtained in the IGT_1 and $Diabetes_1$ group is explicable by the fact that the latter group represented newly diagnosed diabetic subjects, and supports the findings of previously reported studies (Savage et al 1975, Reaven et al 1968, 1976, 1989); the findings in the $Diabetes_1$ group possibly also serves to highlight the concept of hyperinsulinaemia (insulin excess)/insulin resistance as the initial lesion in diabetes.

The evidence for pancreatic secretory defect in IGT subjects was based on the finding that when compared to the control group, the Mean Insulinogenic Index during OGTT was strikingly attenuated in the study group, despite the higher plasma insulin response, with progressively decreasing levels in the 3 study groups ($Normal_1 \rightarrow IGT_1 \rightarrow Diabetes_1$). The argument against this being due solely to the effect of calculation of a ratio (Reaven and Miller 1968), was the finding that the $Normal_1$ group despite having similar glucose response to the Control group, had Insulinogenic Indices lower than those in the Control group.

As regards the effect of obesity on the insulin response, the present study demonstrated no significant difference in plasma insulin response between obese and non-obese in each of the 3 study groups (IGT_1 $Normal_1$ $Diabetes_1$); whilst in the Control group, levels were significantly higher in obese subjects. Therefore, this study has highlighted that the differences in insulin response were probably related to variation in glucose tolerance, rather than obesity.

The association between IGT and macrovascular disease has been highlighted in the present study which has demonstrated a high prevalence of ischaemic heart disease (as indicated by ECG abnormalities) in South African Indian subjects with IGT, and supports the findings of the Bedford and Whitehall studies (Keen et al 1965, Fuller et al 1980). In the present study, this was true whether the study group was examined as a whole (prevalence 35.2%) or when divided according to category of glucose tolerance and compared to the Control group - the prevalence being highest in the IGT_1 group (40.4%), lowest in the Control group (21.9%) (p0.035), and intermediate in the $Diabetes_1$ group (34.2%) and the $Normal_1$ group (30%).

That a high prevalence of IHD was observed even in the Control group is in accordance with previously reported mortality data on CHD in the South African Indian population (Walker ARP 1980, Wyndham et al 1982), and also serves to strengthen the heightened risk for IHD with abnormal glucose tolerance, be it causal or by association. The finding that the prevalence of IHD was higher in the IGT_1 group than in the $Diabetes_1$ group was interesting (similar findings were reported in the Whitehall study) - although this may well be accounted for by the latter group being comprised of newly diagnosed diabetics; however, whether in fact the risk for IHD in South African Indians is higher in subjects with IGT than in those with $Diabetes_1$ is unclear, and would require comparison with subjects with established diabetes.

A further interesting observation in the present study was that the relationship between ECG abnormalities and other selected risk factors for IHD differed in the IGT group and the Control group; in the control group the mean blood pressure and prevalence of hyperlipidaemia, particularly in females, were significantly elevated in subjects with "Abnormal" ECG; whilst, in the IGT_1 group, the mean age, 2-hr plasma glucose, uric acid and prevalence of hyperuricaemia were significantly associated with "Abnormal" ECG. Perhaps, this may have implications in the long term ie. if ECG abnormality is a risk factor for subsequent CHD mortality in subjects with IGT (Fuller et al 1980), and if, as in the present study, IGT_1 subjects with "Abnormal" ECG have higher mean 2-hr plasma glucose, then perhaps intervention programmes in this IGT group may reduce the risk of CHD mortality in such subjects.

The high prevalence of IHD was further supported by the demonstration that 20% of the study subjects tested had positive Exercise Stress Test (EST). Of interest, was that all those subjects with positive EST demonstrated abnormalities indicative of IHD on resting ECG. The obvious limitations in the present study was the small sample size and lack of control subjects for the EST study; clearly what is required is a study which includes larger sample numbers and moreover, of greater value, would be a prospective analysis to determine the predictive power of EST in subjects with IGT.

As regards the lipid profile, the present study has shown and confirmed earlier reports that no major alteration in lipid metabolism exists with IGT; moreover, it has demonstrated that any such alteration is more prevalent in females. Intergroup comparison demonstrated that in female subjects, Mean Serum Total Tg was significantly higher in the IGT_1 group compared to the Control group, whilst serum Total Chol and HDL-chol were similar in the two groups; in males, no difference was observed between the IGT_1 and Control groups, for any of the serum lipids examined. It is true that when the study group was examined as a whole, the Mean Total Chol and Tg were higher than in the Control group; however, this was due to the levels being higher in the $Diabetes_1$ group.

Examination of the relationship between Glycosylated Haemoglobin (HbA1) and OGTT in the present study has demonstrated that the Mean GHb was similar in the Control group and IGT group (Total Study Group and IGT_1); that GHb is relatively insensitive in the detection of IGT (17%) and Diabetes (26%) with considerable overlap between these groups and the Control group; and that GHb is a poor substitute for OGTT in the diagnosis of IGT and Diabetes. This study also highlights the need for uniformity in the methods employed and the fraction of GHb which are measured (as for OGTT), for meaningful comparisons between studies.

The present study demonstrated no significant difference in mean plasma uric acid between the various categories of glucose tolerance (Control group vs Total study group; or Control group vs IGT_1 $Diabetes_1$ $Normal_1$); however the prevalence of hyperuricaemia was high in the IGT_1 and $Diabetes_1$ groups, due mainly to the high prevalence in females. The results of the present study are at variance with other studies which have found raised plasma uric acid in IGT subjects (Herman et al 1976, Tuomilehto et al 1988). However, little information exists regarding the relationship between IGT and uric acid using WHO criteria (Tuomilehto et al 1988), and only confirms the need for further population studies. The negative association between plasma uric acid and Diabetes found in the afore mentioned studies was not confirmed in the present study in which levels were similar in the $Diabetes_1$ and Control groups. It could be argued that these were newly diagnosed diabetics; however, in the Israeli study (Herman et al 1976) even newly diagnosed diabetic subjects has lower plasma uric acid levels compared to non-diabetic subjects; and in the Fijian study (Tuomilehto et al 1988), the mean levels were similar in newly diagnosed and known diabetic subjects.

The association between plasma uric acid and IHD in the present study, has been alluded to earlier. Whether the relationship between glucose tolerance and plasma uric acid/hyperuricaemia is a causal one, or on the basis that both share a common risk association for CHD, is at present unclear.

As regards the natural history of IGT in South African Indians, the present study demonstrated that 50.4% of the subjects progressed to NIDDM over a four year period, with a rate of progression of 12.6% per annum. The results of the present study are at variance with most other published prospective studies on IGT, which report that in less than half, the abnormality progresses to NIDDM within 10 years; and that in the majority, glucose tolerance reverts to normal or persists unchanged (Birmingham Diabetes Suvey Working Party 1970, 1976, Keen et al 1982, Sartor et al 1980, NDDG 1979, Saad et al 1988, King et al 1984, Schrantz AG 1989, Jarrett et al 1979, 1982, Sazaki et al 1982, Kadowaki et al 1984).

That over half of the subjects progressed to NIDDM over the study period, is a progression rate even higher than that found in Pima Indians (31%) and Nauruans (26%), the two populations with the highest prevalence of diabetes mellitus (Saad et al 1988, King et al 1984). The proportion of subjects who persisted with IGT, 24.8%, is similar to that found in the Pima Indians (26%), whilst fewer subjects reverted to Normal glucose tolerance in the present study (24.8%) compared to the Pima Indian study (43%).

Thus the finding in the present study that, using WHO criteria, 50.4% of South African Indians with IGT progressed to NIDDM, is one of the highest recorded in the literature; therefore, in this population group, IGT has significant prognostic implications and should not be ignored.

Of note, is that, strictly speaking, the only other reported prospective population based studies on IGT which have employed WHO criteria, are those on Pima Indians (Saad et al 1988), Nauruans (King et al 1984) and Maltese (Schrantz AG 1989).

Examination of risk factors associated with the high rate of progression to diabetes in South African subjects with IGT has demonstrated that when Year 0 was used as baseline, significant predictors included both fasting (0 min) and 2-hr plasma concentration; when Year 1 was used as baseline the significant predictor was 90-min glucose concentration ie. mid test value.

Thus the results of the present study support those of previously reported studies viz. that of all factors studied, the single most important predictor of subsequent diabetes in subjects with IGT is the baseline plasma glucose concentration; irrespective of the different populations studied, methods employed or the criteria adopted for defining worsening to diabetes.

Whilst the finding that baseline fasting and 2-hr plasma glucose levels are significant predictors is consistent with the majority of the studies reported, an interesting observation in the present study was that when Year 1 was used as baseline, the 90-min plasma glucose (ie. mid-test value) was a significant predictor of subsequent diabetes. This would lend support to the suggestion that in prospective studies of IGT, at least 3 plasma glucose samples during OGTT be examined ie. fasting + 2-hr + mid-test (30, 60 or 90 min) (Modan et al 1989). However, whether subjects should have 3 mid-test values (30, 60 and 90 min) or a single mid-test value (and if so, which mid-test value) is not clear, especially in light of the finding in the present study that the 90 min and not 60 min value was a significant predictor; moreover, there still exists the practical problem of multiple venepunctures in large scale epidemiological studies. Certainly, the finding in the present study emphasises the need for further population-based studies to assess the significance of mid-test glucose values in subjects with IGT.

From analysis of the trend in the proportion of study (IGT) subjects progressing to diabetes across different cut-off levels of baseline blood glucose concentrations, it would appear that in South African

Indian subjects with IGT, the risk of progression to diabetes is total, if baseline 2-hr plasma glucose is ≥ 10.2 mmol/L or if baseline fasting (0 min) plasma glucose is ≥ 7.3 mmol/L.

The present study has allowed for evaluation of the WHO and NDDG criteria for glucose tolerance. The results confirm the few reported studies that the criteria for glucose tolerance have an advantage over those of the NDDG, since it can classify all subjects by way of a simpler, inclusive scheme; requires only 2 blood samples and moreover, its criteria for IGT identified all those subjects at risk for subsequent diabetes. On the other hand, the NDDG requires 5 (or 3 in field studies) blood samples, employs a more complicated classification scheme which includes a large proportion of non-diagnostic OGTT; moreover, the NDDG criteria for IGT failed to identify 18.7% of those subjects who were at risk for subsequent progression to diabetes.

An interesting observation in the present study was that of variability of OGTT results in the same individual at various stages of the study, which might be explained on the basis of the phenomenon of "regressionto the mean", and which will be discussed below.

The introduction of the category of IGT has not been without controversies which have addressed primarily the question of whether IGT warrants being regarded as a separate category or whether it is just one end of a continuum of glucose intolerance (Stern et al 1985, Stern MP 1988, Jarrett RJ 1987, Yudkin et al 1990).

The argument put forward by Jarrett (1987) was that whilst the phenomenon of IGT (or glucose intolerance) is of scientific and clinical interest, that a *category* of IGT is of little value; the principal disadvantages being that (i) IGT is an unstable state and that for eg. in the Bedford Survey, over 10 years, only a minority worsened to NIDDM, the majority reverting to normal glucose tolerance (ii) that the different rates of progression from IGT to NIDDM may be due, in part, to different spectra of blood glucose distribution *within* the IGT category; and (iii) that, whilst one of the reasons for the criteria promulgated by the NDDG was to remove the label "diabetic", the entity of IGT itself, now being used as a diagnosis, was attracting attention, for example, from insurance companies, to the possible detriment of subjects so categorized.

The only advantage of IGT, in his opinion, was that "it is a convenient label" for clinicians to attach to people suspected of having diabetes but who fall short of the diagnostic criteria, often at the risk of ignoring the fact (i) that the risk of progression to diabetes is related to the degree of glucose intolerance and not a simple function of having IGT and (ii) that the risk of CVD is associated with the upper 5% of the blood glucose distribution and not simply with the category of IGT.

What then is the evidence from the present study? This study has confirmed that IGT is an unstable state, as judged by variability of OGTT (vide infra); and that the risk of progression is related to the degree of glucose intolerance within the IGT category. However, the evidence from the present study that over 50% of South African Indians with IGT progressed to diabetes is of concern, and has highlighted differences in the significance of IGT depending on the population group being studied (Mutch and Stowers 1982). As regards cardiovascular disease, an interesting observation in the present study was that the prevalence of IHD was in fact higher in the IGT_1 group than in the $Diabetes_1$ group.

Thus, whilst Jarrett's criticisms are valid, no alternative has been offered. Whether IGT should be regarded as a separate category could be a matter of considerable debate; however, in the absence of an alternative to OGTT, plasma glucose levels would have to be accepted as the basis for diagnosis of the state of glucose tolerance. If so, where should the subjects hitherto classified as IGT belong? If classified as glucose intolerance (present IGT+Diabetes), then perhaps in population groups viz Bedford and Whitehall, in which the risk of progression to diabetes is low, an unnecessary overestimation would result. Evidence from the Pima Indians, Nauruan and Maltese study is that a significant minority progress to diabetes, and therefore certainly, these subjects with IGT cannot be classified as normal. To suggest that different criteria for glucose tolerance be employed for different populations is no alternative (although, if that were so, then the results of the present study would strongly argue in favour of lowering the cut-off level for the diagnosis of diabetes in this population, in light of the fact that the risk of progression to diabetes was total if baseline 2-hr plasma glucose $\geq$ 10.2 mmol/L). Clearly what is required are further studies to highlight the significance of IGT in different populations, before decisions are taken on the fate of IGT as a category.

Stern et al (1985, 1988) suggested that IGT is not a homogeneous category, and, employing the concept of bimodal distribution of 2-hr blood glucose levels (bimodality), proposed that IGT consists of 3 groups which although conceptually distinct, cannot be distinguished by glucose tolerance testing alone, and would probably require the development of a definitive marker for the prediabetic state. The 3 groups proposed include "IGT normals" (upper tail of normal glucose tolerance); "false-negative (FN) diabetics" (lower tail of diabetes) and "IGT in transition" (transition from normal to diabetes). It was also pointed out that only a minority of IGT subjects will belong to the third group ("IGT in transition") - since the implication of bimodality is that the transition state between normal and diabetic is relatively short-lived and that diabetes is not the result of a gradual deterioration of glucose tolerance. A further confounding contribution to this heterogenous nature of IGT is the biochemical measurement (ie. blood glucose level) which is subject to the principle of "regression to the mean" (Fletcher et al 1982) - ie. because of an inevitable degree of error in any measurement, individuals selected from one or other extreme of a distribution will, on repeat measurement, tend to lie closer (ie. regress) to their overall population mean; thus on repeat measurement, "IGT normals" would have lower plasma glucose values, whilst "FN diabetics" would have higher values (ie. values closer to the mean of the normal and diabetic population, respectively).

The results of the present study which have demonstrated, on the basis of OGTT, that over 50% of subjects labelled as IGT progressed to diabetes would imply that in this population, IGT is comprised mainly of "FN diabetics" or "IGT in transition"; moreover, it has highlighted a rapid decompensation to diabetes since 72% of those who progressed to diabetes, did so within the first year, as was observed in Pima Indians (Knowler et al 1981). The rapid decompensation would suggest, if Stern's thesis is to be accepted, that the subjects in the present study belonged to the "IGT in transition" group, rather than "FN diabetic" group who may progress slowly.

The observation in the present study, of variability in OGTT results on repeat testing in the same individual, could probably be explained by the phenomenon of 'regression to the mean'.

Notwithstanding the plausibility of Stern's thesis regarding the heterogeneity of IGT, one concern is that no explanation is offered for a possible fourth group ie. "true IGT" (not IGT intransition but persisters) or does the concept of bimodality preclude such a group? Perhaps what is required is an evaluation of this group of "persisters", to determine whether they possess clinical and/or biochemical characteristics which are distinct.

Another question raised by Stern was whether the increased cardiovascular risk associated with IGT was confined to FN diabetics and IGT intransition, and whether IGT normals were spared. An interesting finding in the present study was that at Year 1, even the $Normal_1$ group (corresponding to Stern's IGT normal) demonstrated a high prevalence of IHD [30% $Normal_1$, 21.9% Control group]. Thus it would appear that the IGT normal group is not spared of the CVD risk. However, it must be noted that this was a cross-sectional analysis of

ECG abnormalities, and perhaps analysis of the prospective data will be more valuable.

Yudkin et al (1990) further commented on the phenomenon of variability of biological response to the glucose load, with respect to its implications regarding the concept of deterioration to diabetes and the instability of the IGT class; their conclusion was that the category of IGT is heterogenous (as suggested by Stern) because of both the interindividual differences in populations as well as the intraindividual variability of the test employed to characterise glucose tolerance; it was therefore suggested that additional criteria be required to categorise subjects with IGT; possibly measurements of insulin and proinsulin molecules.

Their argument was that variability of OGTT had implications both for cross-sectional and prospective studies; that as a consequence of variability, an epidemiological survey may appreciably overestimate the prevalence of both IGT and diabetes in the population studied. As regards the effect of variability in prospective studies, they examined the definition of the criteria for "deterioration to diabetes" in IGT subjects using OGTT, and suggested that perhaps the high rates of deterioration to diabetes may be due to the fact that in most prospective studies, a single OGTT was used, with a resultant overestimation of risk of diabetes in IGT subjects; it was suggested that perhaps a more reasonable approach would be to repeat the GTT on at least 3 occasions, but it was acknowledged that this was unacceptably demanding for both subjects and investigators.

As regards alternatives to OGTT, the role of glycated haemoglobin was reviewed and found to be a poor substitute. The role of insulin in subjects with IGT was highlighted, (hyperinsulinaemia/insulin resistance) and it was suggested that perhaps measures of insulin, might help define the 3 groups of IGT; moreover, they felt that whilst hyperinsulinaemia could be equated with insulin resistance, such a deduction should be treated with reserve, since it is possible that the hyperinsulinaemia is in fact due to elevated concentrations of intact and split proinsulin, and that perhaps insulin deficiency may be a more important contributor to the aetiology of diabetes - however, what remains to be proved is whether "IGT normals" and 'FN diabetics' might be distinguished from patients with true IGT by the use of more sensitive and specific assays for insulin-like molecules.

What is the evidence from the present study? That variability of OGTT exists was confirmed in the present study. That overestimation of the risk of diabetes in the study subjects was due to the fact that the end-point of study was the date of diagnosis of diabetes based on a single OGTT is therefore also plausible. However, since similar criteria were used in other reported studies, viz. Pima Indians, Nauruans, Maltese studies, it would have to be conceded that the risk in this population is more real than apparent. Moreover, if in fact these subjects were at baseline FN diabetics or IGT in transition then at least the present criteria for glucose tolerance allowed for identification of these subjects, who may otherwise have been lost to follow up.

As regards the role of insulin, the present study has demonstrated that although hyperinsulinaemia was a feature of the IGT_1 group, it was also a feature of the $Diabetes_1$ group, and can therefore not be used as a sole arbiter between the groups; moreover, the insulin level was not found to be a predictor of subsequent diabetes. Clearly what is required is analysis of existing data, to determine whether the risk for diabetes can be predicted on the basis of low and high insulin responders in the IGT_1 group. An argument against the $Normal_1$ group being merely "IGT normals" who returned to their biological set point at Year 1, was the observation that despite the glucose levels being similar in the $Normal_1$ group and Control group, the Insulinogenic Indices were lower in the $Normal_1$ group compared to the Control group; implying perhaps that there is some defect in insulin secretory capacity.

Thus whilst the criticisms of the three sets of review are valid and highlight the inconsistencies regarding the present criteria for glucose tolerance, there are obviously no clear answers at present, thus highlighting the need for further studies.

Inherent in the diagnosis of diabetes and other categories of glucose tolerance is the blood glucose value, and since to date, there appears to be insufficient data to support the use of insulin response as an alternative to OGTT, it would have to be conceded that, in the absence of a definite alternative, the OGTT will have to be continued to employed, at the risk of overestimation of the prevalence of glucose intolerance.

Also, the increasing data to support the value of early detection and appropriate management of diabetes before the onset of its complications (WHO 1985), would appear to argue in support of perhaps overestimation of the prevalence of glucose intolerance.

It is surprising that whilst recommendations have been proposed on the criteria for adequate control based on blood glucose levels (WHO 1985), which of necessity are in themselves arbitrary, recommendations with respect to cut off levels for the diagnosis of states of glucose tolerance, are viewed with greater criticism. It would have to be accepted that any criteria based on a biochemical value (viz blood glucose) would have to be, in a way, arbitrary.

The question of whether IGT be regarded as a separate category or that it be considered as just one end of a continuum of glucose intolerance has been addressed above and has highlighted the fact that should this category be dispensed with, a revision of the presently employed criteria for the diagnosis of the different states of glucose tolerance will be necessitated, especially in view of the fact that the significance of IGT (with respect to progression to diabetes) differs depending on the populations groups studied. Certainly, in the light of the findings in the present study that a significant proportion of IGT subjects progressed to diabetes, it would appear that in this population, if the category of IGT be dispensed with, then in fact the cut-off levels for diabetes (or glucose intolerance) in this population be lowered (in view of the fact that all those subjects with baseline 2-hr plasma glucose $\geq$ 10.2 mmol/L, progressed to diabetes).

In conclusion therefore this prospective study on South African Indians with IGT has served to highlight the clinical and biochemical parameters associated with IGT in this population; moreover the study has demonstrated that since in South African Indians the risk of progression to diabetes is high, IGT has significant prognostic implications.

Notwithstanding the limitations of any prospective population-based study, it is hoped that this study has at least covered the scope of the thesis. The cross-sectional data have served to demonstrate that in South African Indians, IGT is associated with increased age, body mass index and blood pressure. These subjects have been observed to exhibit hyperinsulinaemia (insulin resistance) as well as possible pancreatic secretory defect; moreover this study has confirmed the association between IGT and cardiovascular disease, as demonstrated by the high prevalence of IHD.

The data from the prospective analysis have highlighted the strikingly high risk of progression to diabetes in South African Indians with IGT, and have served to identify those risk factors associated with the high rate of progression.

The present study has allowed for examination of the currently employed diagnostic criteria for IGT, and the results are supportive of the WHO criteria, but also raise certain questions viz. the value of mid-test samples.

As regards the question of whether IGT be regarded as a separate entity, evidence from the present study and other reported studies, would argue in favour of its retention, primarily because of the different risks of progression to diabetes in different populations; moreover, if this category be considered dispensable, then perhaps it would necessitate a review of the presently employed cut-off levels [of blood glucose concentration] for the diagnosis of diabetes.

Clearly, this study confirms the need, not only for further analysis of existing data from the present study, but also the need for further population based studies, before decisions are made on the fate of IGT.

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ABBREVIATIONS

ANOVA	analysis of variance.
BMI	body mass index.
BDSWP	Birmingham Diabetes Survey Working Party.
CHD	coronary heart disease
CVD	cardio vascular disease
CHO	carbohydrate
chol	cholesterol
ECG	electrocardiogram
EST	exercise stress test
FBG	fasting blood glucose
Ghb	glycosylated haemoglobin
HDL-chol	high-density lipoprotein cholesterol
HLA	histocompatibility antigen
HbA_1	haemoglobin A_1
IGT	Impaired glucose tolerance
II	Insulinogenic Index
IHD	ischaemic heart disease
log	logarithm
NDDG	National Diabetes Data Group
NIDDM	Non-insulin dependent diabetes mellitus
OGTT	oral glucose tolerance test
Tg	triglyceride
USPHS	United States Pulbic Health Service
WHO	World Health Organisation
w.t.d.	worsening to diabetes