Impaired Glucose Tolerance : 5-year Follow - up

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INTRODUCTION

Classification of subjects into different categories of glucose tolerance has clinical significance. The present WHO classification [1] into normal, impaired glucose tolerant and diabetic is based on epidemiological studies relating the outcome (morbidity and mortality) to plasma glucose levels [2], supported by the bimodal distribution of plasma glucose levels in populations with very high prevalence of diabetes [3]. Expectedly, the twilight zone of IGT has generated much debate and arguments [4]. Diabetes in the developing countries has different aspects than those described in the developed countries [5]. Many developing countries show a high prevalence of IGT [6] and it is thought that this represents a stage in the evolution of metabolic and vascular morbidity in these populations. There have been a few reports of IGT, especially long term follow-up studies in the Indian literature[7]. In this paper, we describe the clinical features, biochemical and endocrine characteristics and follow-up of glucose tolerance over 5-years in subjects with IGT.

Subjects And Methods

This data was collected in the Wellcome Diabetes Study, a prospective study of subjects with different degrees of glucose tolerance. The study design has been reported [8]. In short, newly diagnosed, untreated hyperglycaemic subjects from the outpatient departments and wards of the K.E.M. Hospital, Pune were serially enrolled. The following subjects were excluded; age>65 years, pregnant women, history of recent (last 6 months) myocardial infarction or stroke, other severe illness (cancer, renal failure, etc.) and those on steroid treatment. Approximately 10% of the eligible subjects declined to participate in the study. Non -diabetic control subjects had either been outpatients for various minor illness (n=101), or were spouses of patients (n=16) or hospital staff (n=16) who responded to our appeal for volunteers; none of these had a known family history of diabetes. Subjects with impaired glucose tolerance (IGT) included 45 outpatient volunteers (including 9 spouses of diabetic patients) and 34 referred to us for an oral glucose tolerance test (OGTT) because of at least one symptom commonly associated with diabetes (polyuria, polydipsia, polyphagia, weight loss or genital symptoms) and/or a family history of diabetes. Thus, there were 133 non-diabetic controls, 79 IGT subjects and 189 Type 2 diabetic patients classified by WHO criteria (1985) for a 75g (anhydrous glucose) OGTT. Clinical examination included anthropometry (height, weight, waist-hip ratio) and blood pressure measurement in supine position. Plasma total cholesterol and triglyceride concentrations were measured on a fasting venous blood sample . plasma glucose (glucose oxidase) and plasma immunoreactive insulin (double antibody radioimmunoassay [9]) concentrations were measured serially during an OGTT. Indices of pancreatic beta-cell function and insulin sensitivity were calculated from the fasting concentrations of plasma glucose and plasma IRI by homeostasis model assessment (HOMA) [10].

Results of the biochemical and other tests were discussed with all subjects and appropriate treatment was prescribed. Subjects were followed up at regular intervals for clinical and biochemical testing and advised as necessary. Clinical examination , biochemical parameters and OGTT were repeated at 5 year follow-up. One hundred and fifty seven NIDDM patients (83%), 59 IGT subjects (75%) and 80 non diabetic controls (60%) were studied at 5-years, others were lost to follow up for various reasons.

The data is presented as a median. Statistical differences between the categories of subjects was tested by Mann-Whitney test and those between initial and 5-year follow up by paired Wilcoxon test. Data was normalised by logarithmic transformation wherever appropriate. Statistical analyses were performed using SPSS. PC +(3.1)package (SPSS Inc., Chicago, lllinois, USA)

Results

Table 1
characteristics of newly diagnosed hyperglycaemic subjects

	Non-diabetic (133)	**IGT** (79)	**Diabetic** (189)
Men %	57	56	65
Age (yr)	40	47	43
Body Mass Index(kg/m^2)			
Men	23.3	25.5	23.9
Women	23.6	26.6	24.9
Waist-Hip Ratio			
Men	0.88	0.93	0.92
Women	0.77	0.79	0.80
Blood Pressure(mmHg)	121/83	129/85	129/87
Plasma Cholesterol(mg/dl)	163	180	167
Plasma Triglycerides (mg/dl)	79	104	126
Plasma NEFA(mmol/L)	0.81	1.02	1.02
Plasma Immunoreactive Insulin (mU/L)			
Fasting	7.5	11.0	16.0
2-hr post glucose (OGTT)	82.5	148.0	55.5

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Table 1 compares the clinical, biochemical and endocrine characteristics in subjects with different categories of glucose tolerance.

Table 2
Cardiovascular risk factors, glucose tolerance and ischaemic electrocardiograms (ECG'S) at diagnosis

	Non-diabetic (%)	IGT (%)	Diabetic (%)
Obese			
Men	15	30	22
Women	40	71	47
Hypertensive	7	28	25
Cholesterol>240mg/dl	5	5	6
Triglycerides>150mg/dl	15	28	38
Ischaemic ECG,s (Minnesota code)			
Men	3	16	11
Women	12	18	23

Table 2 highlights that, there is an excess of obesity, hypertriglyceridaemia, hypertension and ischaemic electrocardiograms in the IGT subjects, even at the time of diagnosis. In these respects, they are similar to diabetics rather than non-diabetic subjects.

An important observation is the change in glucose tolerance over a 5-year follow-up period. Of the 80 subjects who showed normal glucose tolerance at initial assessment, 14 (18%) showed a deterioration to IGT and in 3(4%) it had deteriorated to diabetes; the remaining 63(78%) showed normal glucose tolerance at 5 year follow-up. Of the 59, initial IGT subjects, 25 (42%) improved to normal glucose tolerance at 5-year, 21 (36%) remained IGT, while 13(22%) deteriorated to diabetes. Of the 157 subjects originally classified diabetic, 6 (4%) showed normal glucose tolerance, 24(15%) were IGT while 126 (80%) remained diabetic.

Table 3
IGT subjects : parameters at diagnosis

5 yr Category n	Non-diabetic 25 (16M)	IGT 21 (10M)	Diabetic 13 (8M)
Age (yr)	-		
Height (m)	1.57	1.57	1.61
Weight (Kg)	64	68	72*
BMI(Kg/m2)	25.8	25.2	26.9
Systoloc BP (mmHg)	123	128	130
Diastolic BP (mmHg)	80	86	90*
Cholesterol (mg%)	187	181	178
Triglycerides (mg%)	79	114	147*
Plasma Glucose (mg%)			
Fasting	95	94	93
2hr OGTT	152	172*	181*
Plasma IRI (mU/L)			
Fasting	10	11	14
2hr OGTT	154	158	159
β-cell function (%)	125	134	145
Sensitivity (%)	41	32	28

All values are Medians * Compare to Non-diabetics

Table 3 compares the clinical and biochemical parameters at diagnosis in subjects who had IGT at diagnosis by their 5-year category (normal, IGT or diabetes). Those with normal glucose tolerance at 5-yr. were lighter (85 Vs 72 kg), had lower 2-hr plasma glucose concentration (152 Vs 181 mg%) during OGTT and lower diastolic blood pressure (80 Vs 90 mm Hg) and plasma triglyceride concentrations (79 vs 147 mg%, all $p<0.05$) at diagnosis as compared to those who deteriorated to diabetes. The indices of pancreatic β-cell function and insulin sensitivity did not differ significantly in the two groups.

Table 4
IGT Subjects : parameters at 5 year follow up

5 yr Category n	Non-diabetic 25 (16M)	IGT 21 (10M)	Diabetic 13 (8M)
Weight (Kg)	63	68	71.5*
BMI(Kg/m2)	25.6	26.5*	27.9*
Systoloc BP (mmHg)	130	142*	136
Diastolic BP (mmHg)	80	84	88
Cholesterol (mg%)	170#	183	165
Triglycerides (mg%)	111	111	128#
Plasma Glucose (mg%)			
Fasting	85#	93*	124*,+,#
2hr OGTT	112#	179*	236*,+,#
Plasma IRI (mU/L)			
Fasting	2#	7	9#
2hr OGTT	71#	173#	109#
β-cell function (%)	68	113#	59#
Sensitivity (%)	140	43	43

Medians
* compared to Non-diabetic + compared to IGT
# Compared to parameters at diagnosis (Table 3)

Table 4 shows the parameters at 5-year follow-up in these groups. Plasma IRI concentrations showed a significant decrease in those who became non diabetic as well as in those who deteriorated to diabetes as compared to the concentrations at diagnosis. β-cell function had deteriorated (145 vs 59%, $p<0.05$) in subjects who became diabetic and in those who continued as IGT. Insulin sensitivity showed improvement (41 vs 140%) in subjects whose glucose tolerance became normal at 5-years; although the improvement was not statistically significant.

Discussion

Our results show an increase in cardiovascular risk factors in subjects with IGT, they are closer to diabetic than non-diabetic subjects in this respect. Our IGT subjects were the most obese of the three groups, had higher blood pressure, circulating lipids and ischaemic electrocardiograms compared to the non-diabetic subjects. It is well known that a proportion of these IGT subjects will ultimately develop diabetes. This suggests that different cardiovascular risk factors are present for a long time before diagnosis in

diabetic patients. Similar findings have been reported earlier[11].

We have shown the liability of glucose tolerance over a period of time, especially in the IGT subjects. Thus, during 5 year period, 42% IGT subjects improved to normal glucose tolerance while 22% developed diabetes. These figures compared well with the earlier prospective studies of IGT which showed that upto 5% subjects deteriorate to diabetes every year[12].

The improvement in glucose tolerance could be ascribed to improved insulin sensitivity, possibly related to better lifestyle (diet and physical exercise) as a result of the advice offered at the initial testing. It is also important that their β-cell function did not deteriorate during the follow up period.

IGT subjects who deteriorated to diabetes were more obese, more hyperglycaemic and had higher diastolic blood pressure and plasma triglyceride concentrations at diagnosis as compared to those who showed improvement in glucose tolerance. These parameters may therefore, be viewed as the 'predictors' for development of diabetes in the IGT subjects. This constellation of clinical and metabolic abnormalities is commonly known as 'syndrome X' or 'insulin resistance syndrome'[13]. Our observations suggest that when IGT co-exists with other components of 'syndrome X', it is likely to progress to diabetes over a period of time.

It is interesting that the deterioration from IGT to NIDDM is associated with progressive β-cell failure and not with the worsening of insulin resistance. Insulin sensitivity, in fact, tended to improve during the 5-years in our IGT subjects, presumably because of the advice that they received (diet and exercise). Thus, diabetes seems to develop in those insulin resistant subjects whose β-cell function shows progressive and significant decline. The exact determinants of β-cell failure, genetic and/or environmental, are not yet known.

In summary, we have shown that IGT subjects from India have an excess of cardiovascular risk factors despite their young age. Obesity, hypertension, hypertriglyceridaemia and the degree of hyperglycaemia at the time of diagnosis are associated with deterioration of glucose tolerance over a period of 5-years. The development of diabetes is associated with progressive β-cell failure. There is a need to apply this knowledge to work out strategies for the primary prevention of NIDDM.

REFERENCES

1. World Health Organisation Study Group. Diabetes Mellitus WHO Tech Rep Ser 1985; 727.

2. Fuller JH,Shipley MJ,Rose G, Jarrett RJ, Keen H. Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall study. Lancet 1980;1:1373-6.

3. Zimmet P, Whitehouse S. Bimodality of fasting and two hour glucose tolerance distributions in a Micronesian population. Diabetes 1978; 27: 793-800.

4. Yudkin JS, Alberti KGMM, Mclarty DG, Swai ABM. Impaired glucose tolerance: is it risk factor for diabetes or a diagnostic ragbag? BMJ 1990; 301:397-401.

5. Yajnik CS. Diabetes in tropical developing countries. In : Diabetes Annual/5. Alberti KGMM, Krall LP (eds). Eelsevier, Amsterdam 1990; 72-87.

6. Ramchandran A.Epidemiology of Diabetes in Indians. Int J Diab Dev Countries 1993; 13:65-7.

7. Ramchandran A, Snehalata C, Naik RAS, Mohan V, Shobhana R, Vishwanathan M. Significance of impaired glucose tolerance in an Asian Indian population : a follow-up study. Diab Res Clin Pract 1986; 2: 173-8.

8. Shelgikar KM, Hockaday TDR Yajnik CS, Central rather than generalised obesity is related to hyperglycaemia in Asian Indian subjects. Diab Med 1991; 8: 712-7.

9. Morgan CR, Lazarow A. Immunoassay of insulin: Two antibody system. Plasma insulin levels in normal, sub diabetic and diabetic rats. Daibetes 1963; 12: 115-26.

10. Matthews DR, Hosker JP, Rudenski A, Naylor BA, Treacher D, Turner RC. Homeostasis model assessment : insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. Diabeologia 1985; 28: 412-9

11. Burchfiel CM, Hamman RF, Marshall JA ,Baxter J, Khan LB, Amirani JJ. Cardiovascular risk factors and impaired glucose tolerance : the San Luis Valley diabetes study. Am J Epidemiol 1990; 131: 57-70

12. Jarrett RJ, Keen H, McCartney P. The whitehall study: ten year follow up report on men with impaired glucose tolerance : the San Luis Valley diabetes study. Am J Epidemiol 1990; 131: 57-70.

13. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-1607.