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Metabolic Profile of Persons with Newly Diagnosed Diabetes Using either Glycoslated Haemoglobin or Oral Glucose Tolerance Test in Primary Prevention Trials in Asian Indians

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Abstract

Background: To compare cardio metabolic characteristics of Asian Indians with incident type 2 diabetes diagnosed by Oral Glucose Tolerance Test (OGTT) or by Glycosylated Haemoglobin (HbA1c).

Research Design and Methods: Data from two Indian Diabetes Prevention Studies in persons with Impaired Glucose Tolerance (IGT) was used. In 314 persons, diabetes was diagnosed by OGTT and another 67 persons had only HbA1c values ≥ 6.5% (≥48 mmol/mol). Cardiometabolic characteristics were compared in 3 sub-groups-1: Persons with positive OGTT only (HbA1c<6.5% (<48 mmol/mol) (n=125), 2: Persons with positive HbA1c but negative OGTT (n=67), 3: Those with both HbA1c and OGTT positive (n=189).

Results: Diagnostic sensitivity of HbA1c was 67.2% when compared with OGTT criteria. Prevalence of obesity, abdominal obesity, hypertension, insulin resistance and lipid abnormalities were similar in all groups. Persons in groups-1 and 2 had similar metabolic characteristics, but for higher plasma glucose in the former group and higher HbA1c in the latter group. Prevalence of abnormalities was similar in both groups. Group with both the tests positive, had higher levels of insulin resistance.

Conclusion: Metabolic characteristics of incident diabetic cases identified either by OGTT or by HbA1c were similar, except for a higher prevalence of insulin resistance among those who had both tests positive.

Keywords: Diagnosis of diabetes; Glycoslated haemoglobin; Incident diabetes; Metabolic profile; Oral glucose tolerance test; Dyslipidaemia; Cardiometabolic abnormalities

Abbreviations

2hrPG: 2hr Plasma Glucose; ADA : American Diabetes Association; BMI: Body Mass Index; EASD: European Association for Study of Diabetes; FPG: Fasting Plasma Glucose; HbA1c: Glycosylated Haemoglobin; HDL-Chol: High Density Lipoprotein Cholesterol; IDF: International Diabetes Federation; IGT: Impaired Glucose Tolerance; LDL-Chol: Low Density Lipoprotein Cholesterol; LSM: Lifestyle Modification; OGTT: Oral Glucose Tolerance Test; T-Chol: Total Cholesterol; TG: Triglycerides; WC: Waist Circumference; WHO: World Health Organization

Introduction

The debate over an ideal robust biochemical test for diagnosing diabetes continues. Blood glucose estimations, either a fasting glucose or an oral glucose tolerance test (OGTT) was considered as "the gold standard" measurement until 2010. Measurement of blood glucose levels are indices of acute changes in relation to food ingestion. Measurement of glycosylated haemoglobin (HbA1c) equals to assessments of multiple blood glucose (fasting and post prandial) values over a period of 2 to 3 months and therefore is a more robust estimation of average glycaemic status. A diagnostic tool gauging chronic rather than spot hyperglycaemia is certainly preferable [1].

It was only in 2008 an International Committee convened by the American Diabetes Association (ADA), the European Association for Study of Diabetes (EASD) and the International Diabetes Federation (IDF) evaluated the pros and cons of using HbA1c as an a diagnostic tool for diabetes [2] and the ADA [3] and the World Health Organization (WHO) [4] recommended its use for the diagnosis. Sensitivity of HbA1c with a diagnostic cutoff of ≥6.5% (≥48 mmol/mol) is considered to be significantly lower than that of an OGTT [5-16]. In Asian Indians, the sensitivity of HbA1c to identify incident diabetes was found to be only 51% when the results were compared with the OGTT [17]. Another study in Chennai, India showed a sensitivity of 78.2% to identify new cases of diabetes in a cross-sectional population survey [18]. However, whether a HbA1c or an OGTT test is superior in identifying persons with diabetes depends on the definition of diabetes. Variations in laboratory measurements and in rate of glycation of proteins can influence HbA1c values. HbA1c values could also be normal in cases with short duration of hyperglycaemia. If diabetes is considered to be a disease only of the glucose metabolism, an OGTT would appear to be an ideal test. Considering the high degree of non reproducibility of OGTT, HbA1c would be a better glycaemic index of the long term presence of hyperglycaemic values. HbA1c also shows strong correlations with diabetic complications [19].

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In this analysis we compared the cardiometabolic characteristics of Asian Indian persons with incident diabetes, and the diagnosis had been made based on the OGTT criteria [20] or by the HbA1c criteria.

Research Design and Methods

The study samples were derived from two Indian Diabetes Prevention Studies; the Indian Diabetes Prevention Program-1 (IDPP-1) and the Indian Diabetes Prevention Program-2 (IDPP-2), the primary results of both were published [21,22]. The studies were approved by the Institutional Ethics Committee. All participants gave written informed consent. In these studies a total of 845 participants with persistant Impaired Glucose Tolerance (IGT) on 2 OGTTs, were followed up for a period of 3 years with assessment of the glycaemic status of all participants at 6 monthly intervals. In these randomized controlled trials, the impact of lifestyle modification (LSM) or use of metformin [21] or LSM and pioglitazone [22] for primary prevention of diabetes was compared with a control group which received standard lifestyle advice only at baseline. All cases included in the analysis (n=381, men:women 314:67) had OGTT and also HbA1c measurements. In the original studies [21,22] the diagnosis of diabetes was made based on the WHO criteria [20]. In this analysis, cases of incident diabetes diagnosed using the WHO criteria for OGTT [20] irrespective of the HbA1c values (Fasting Plasma Glucose (FPG) was ≥126 mg/dl and /or the 2hr plasma glucose (2 hr PG) value was ≥200 mg/dl (n=314)), and another group of 67 persons who had non-diabetic range of glycaemia on GTT, but had HbA1c values diagnostic of diabetes ≥ 6.5% (≥48 mmol/mol[3]) were included for the comparisons. Therefore a total of 381 participants were included in the analysis.

Measurements of height, weight, body mass index (BMI) (kg/m^2), waist circumference (WC) and measurement of blood pressure were done by standard methods.

Fasting and 120 minutes plasma glucose values were measured (glucose oxidase method using auto analyzer, Roche 911, Germany) and corresponding plasma insulin was measured using a radioimmunoassay kit from DiaSorin (Saluggia, Italy). Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR). A value ≥ 4.1 was considered abnormal for our population [23]. Fasting lipid profile consisting of total cholesterol (T-Chol), LDL-cholesterol (LDL-Chol), HDL-cholesterol (HDL-Chol) and triglycerides (TG) were measured by enzymatic procedures (Reagents of Roche Diagnostics, Germany). HbA1c was analyzed using the immunoturbidimetric method (Tina-Quant Reagents; Roche Diagnostics GmbH, Mannheim, Germany). This method shows good correlation with the high performance liquid chromatography method (r = 0.9937) and is an approved procedure by the International Federation of Clinical Chemistry, certified by the National Glycohemoglobin Standardization Procedure and traceable to the Diabetes Control and Complications Trial assay procedure. The intra-batch coefficient variation of HbA1c was <5% (<31 mmol/mol) and inter-batch variation was <7% (<53 mmol/mol).

Presence of hypertension (≥130/85 mmHg), newly diagnosed or known cases on medication were recorded. T-Chol of ≥200.8 mg/dl, HDL-Chol ≤ 40.2 mg/dl, LDL-Chol ≥ 100.4 mg/dl, and TG ≥ 150.4 mg/dl were considered as abnormal. BMI ≥ 25 kg/m^2 was indicative of obesity and WC ≥ 90 cm for men and ≥80 cm for women indicated abdominal obesity. A comparative assessment of abnormal anthropometric and metabolic parameters was made in persons categorized as shown below.

Group-1: Persons with diabetes who had positive OGTT but with HbA1c<6.5% (48 mmol/mol) (n=125)

Group-2: Person with negative OGTT but with HbA1c ≥ 6.5% (≥48 mmol/mol) (n=67)

Group-3: Persons satisfying both OGTT and HbA1c criteria for diabetes (n=189)

There was no overlap of persons in any group. The median follow up period until diagnosis of diabetes were 24 months, 30 months, and 18 months for groups 1,2 and 3 respectively. Figure 1 shows the total number of participants in each group and also the numbers available from IDPP-1 and IDPP-2 trials.

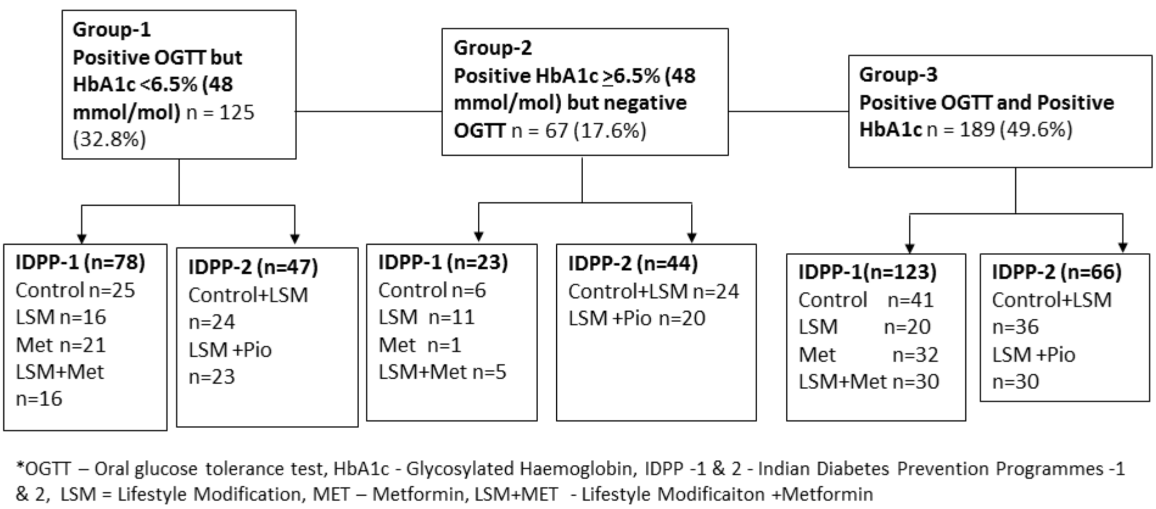

Figure 1: Description of the study groups, number of participants selected from IDPP-1 and IDPP-2 trials.

Statistical Analysis

Mean + SD are reported for normally distributed variables. Median values are shown for TG as it showed skewed distribution variables. One way ANOVA was used for group comparison of normally distributed variables. Intergroup comparisons were done by student's unpaired 't' test. For TG, the Kruskal-Wallis non-parametric test was applied for group comparison. Chi-square test was used to compare the proportions of abnormalities between groups. Prevalence of metabolic abnormalities were compared between men and women. Homeostatis model assessment (HOMA-IR) was used for deriving insulin resistance). HOMA-IR was calculated using the formula: ((fasting insulin(mU/L) × fasting glucose(mmol/L)) / 22.5)). HOMA-IR values were measured only in a subsample in which blood samples were available [24].

Results

The distribution of persons with diabetes in the three study groups is shown in Table 1. Among the total of 381 persons, 256 (67.2%) had the diagnostic HbA1c value also. Therefore, considering OGTT as the standard criteria, the sensitivity of HbA1c in this study cohort was 67.2%. Of the total 381, 189 participants (49.6%) had satisfied both diagnostic criteria. Among the total 381 persons, 314 had 2h glucose values ≥ 200 mg/dl and 98 persons had fasting plasma glucose ≥ 126 mg/dl.

Variables	Group-1	Group-2	Group-3	p value			
	Only Positive OGTT (n=125)	Only Positive HbA1c (n=67)	OGTT and HbA1c Positive (n=189)	(One-Way ANOVA)	Group 1 Vs 2	Group 2 Vs 3	Group 1 Vs 3
	Mean ± SD						
Age (baseline) (years)	46.1 + 5.8	46.2 + 5.7	45.8 + 5.5	0.859	0.834	0.602	0.723
Body Mass Index (Kg/m^2)	26.1 + 3.3	26.4+ 3.9	26.7 + 3.6	0.352	0.652	0.512	0.144
Waist Circumference (cm)	91.0 + 7.8	89.1+ 7.0	92.2 + 9.0	0.036	0.094	0.013	0.258
Blood Pressure (mmHg) Systolic	118.6 + 11.1	121.0 + 11.7	122.8 + 12.0	0.008	0.157	0.301	0.002
Diastolic	80.2 + 9.3	78.7 + 8.7	77.6 + 9.0	0.043	0.267	0.389	0.013
Plasma Glucose (mg/dl) Fasting	110.8 + 15.2	107.8 + 9.6	126.0 + 28.3	<0.0001	0.142	<0.0001	<0.0001
120 min	223.6 + 26.1	154.9 + 31.2	247.2 + 42.9	<0.0001	<0.0001	<0.0001	<0.0001
HbA1c % (mmol/mol)	6.0+0.3 (41.6+ 3.4)	6.8 + 0.3 (50.4 + 3.3)	7.4 + 0.8 (57.1 + 8.9)	<0.0001	<0.0001	<0.0001	<0.0001
HOMA-IR†	5.8 (n=114)	4.3 (n=28)	6.3 (n=154)	0.003	0.044	<0.0001	0.059
Lipid Profile (mg/dl) Cholesterol	199.7 + 39.5	188.0 + 32.9	200.5 + 37.2	0.054	0.040	0.016	0.864
Triglycerides†	146	133	150	0.713	0.700	0.395	0.703
HDL-Cholesterol	42.8 + 8.9	40.5 + 9.8	41.8+ 8.5	0.207	0.094	0.311	0.280
LDL-cholesterol	122.5 + 37.1	114.7 + 31.1	122.0+ 37.6	0.306	0.141	0.156	0.892

†Median test; OGTT- Oral Glucose Tolerance Test; HbA1c – Glycoslated Haemoglobin

Table 1: Metabolic characteristics of persons with diabetes diagnosed based only on OGTT (Group-1), those with only positive HbA1c (Group-2) and those satisfying both criteria (Group-3).

Use of OGTT or HbA1c criteria identified different people with diabetes. The metabolic characteristics of group-1: (only OGTT Positive), group-2: (HbA1c Positive) and group-3: (Both OGTT and HbA1c positive) are shown in Table 1. It was noted that BMI and the lipid profile values were similar in all categories of persons. As expected the glycaemic parameters were significantly higher in people who satisfied both the criteria. Persons in group-2 had significantly lower (P<0.05) values for WC, glycaemic parameters, HOMA-IR, HbA1c and cholesterol values than group-3. Table 2 shows the metabolic characteristics and percentage of abnormal cardiometabolic variables in the study groups. Prevalence of obesity, abdominal obesity, new and known hypertension and lipid abnormalities were similar in these groups. Prevalence of increased HOMA-IR was higher in group-3 than the other groups.

Variables	Group-1		Group-2		Group-3		p value
	Only Positive OGTT (n=125)		Only Positive HbA1c (n=67)		OGTT and HbA1c Positive (n=189)		
	n	%	n	%	n	%	
Body Mass Index ≥ 25 (kg/m^2)	72	57.6	43	64.2	127	67.2	0.223
Waist Circumference Men ≥ 90 (cm) Women ≥ 80 (cm)	59 12	53.2 85.7	27 19	60.0 86.4	95 24	60.1 77.4	0.492 0.651
Cholesterol ≥ 200 (mg/dl)	57	45.6	23	34.3	90	47.6	0.165
Triglycerides ≥ 150 (mg/dl)	60	48.0	28	41.8	96	50.8	0.447
HDL-Cholesterol ≤ 40 (mg/dl)	53	42.4	37	55.2	96	51.1	0.178
LDL-cholesterol ≥ 100 (mg/dl)	99	79.2	50	74.6	145	77.1	0.756
Hypertension							
New	17	13.6	10	14.9	26	13.8	0.965
Known	14	11.2	8	11.9	22	11.6	0.987
HOMA-IR ≥ 4.1	78	68.4	16	57.1	124	80.5	0.010
OGTT- Oral Glucose Tolerance Test; HbA1c - Glycoslated Haemoglobin							

Table 2: Prevalence of cardiometabolic abnormalities among the study groups.

The comparative assessment of the abnormalities among men and women showed that prevalence of obesity was increased among females in group-1 (men 61%, women 77.8%, χ^2=4.0, p=0.046) and presence of higher WC was more among women in groups 2 and 3 (men 57.2%, women 84.4% (χ^2=10.9, p<0.0001). Prevalence of dyslipidaemia and hypertension were similar among men and women.

Discussion

This analysis in a fairly large number of incident diabetic cases available from prospective analysis of persons with IGT showed that the metabolic characteristics of the persons identified either by OGTT or by HbA1c were largely similar. Among the 381 persons diagnosed with diabetes by one of the two criteria, only 189 (49.6%) satisfied both the criteria. Sensitivity of HbA1c for diagnosing OGTT positive cases was 67.2% (256/381 cases). Several studies in populations of varied ethnicity and races had reported significantly lower sensitivity for HbA1c to detect diabetes when compared with OGTT [5-16]. OGTT and HbA1c categorized different persons with diabetes. The discordance between OGTT and HbA1c results occurred because the latter was compared with the OGTT results used as a gold standard.

The persons identified by the two diagnostic criteria will remain discordant to some extent as OGTT indicates acute changes in blood glucose levels while HbA1c is an index of long-term process of glycosylation and therefore they hallmark different physiological processes. Many cases with recent hyperglycaemia are unlikely to have the diagnostic levels of HbA1c for diabetes. Moreover ethnic variations in the rate of glycosylation might also affect the sensitivity of HbA1c as a diagnostic tool for diabetes [10,25,26].

We noted that the metabolic characteristics and cardiovascular risk profile of the incident diabetic cases diagnosed by either the OGTT or by the HbA1c criteria were similar in the Asian Indian population. Presence of insulin resistance was more common in persons positive for both diagnostic criteria. This could be related to the higher levels of fasting and postprandial plasma glucose values. Prevalence of obesity was also more in this group although the difference from the other two groups were not statistically significant.

Several studies [10,11,13,27-29] in varied ethnic populations had reported that diabetes diagnosed by HbA1c had higher age, BMI, lipid levels and insulin resistance than those diagnosed by OGTT. A study in Chinese population had reported more unfavourable cardiovascular and metabolic profile among those who had HbA1c ≥ 6.5% (≥48 mmol/mol) especially among the OGTT negative population [27]. The diagnostic sensitivity of HbA1c was reported to be 66.8% in this population, a value similar to that in our study. Vlaar et al. [11] screened 944 south Asians in Hague, Netherland (18-60 year old), with OGTT and HbA1c for diabetes and prediabetes. The overlap between the two criteria was partial both for diabetes and prediabetes. However the metabolic risk profiles were identical in the group identified by the different criteria.

Borg et al. [12] noted that the HbA1c and OGTT criteria identified similar prevalence of risk profiles in the Danish population. They reported HbA1c identified higher proportion (6.6%) of undiagnosed diabetes than OGTT (4.1%) in the population of the Danish Inter 99 Study. This was contrary to the observation of several other studies which reported lower sensitivity for HbA1c to diagnose diabetic cases [10,11,13,27-29]. Major population-based epidemiological studies have demonstrated a lower prevalence of diabetes by HbA1c criteria compared with OGTT [5,6,16].

Our cohort of persons with diabetes were collected from prospective studies and were newly diagnosed with not more than 6 months of duration. The participants underwent diagnostic tests for diabetes at 6 monthly intervals as all of them had IGT at the baseline. Cross sectional studies have the disadvantage that some may have undetected diabetes of varied durations with consequent metabolic changes.

High prevalence of metabolic abnormalities including overweight/obesity and insulin resistance was due to selection of persons with persistent IGT and also due to the selection of persons with other risk factors for diabetes.

This analysis in Asian Indian persons with type 2 diabetes (n=381), identified during the three year prospective analysis of IGT indicated that, although there was discordance among the diabetic groups diagnosed by the OGTT or HbA1c criteria, most of the cardiometabolic characteristics were similar. It was a limitation that there was a male predominance of (82.4%) in this study. However, a comparison of the metabolic characteristics of men and women in group-1 and 2 did not show significant gender differences. It was also noted that the prevalence of cardiometabolic abnormalities other than abdominal obesity was similar among men and women. It is well known that among middle aged men and women, abdominal obesity is higher in women [30].

As observed in many studies among varied populations, we also noted that OGTT and HbA1c identified different groups of persons with diabetes, with an overlap of about 50-60%.

As we had selected persons with IGT, prevalence of metabolic abnormalities was high. Although we had selected persons with risk factors for diabetes, the prevalence of cardiometabolic abnormalities were similar among persons diagnosed with diabetes either by using HbA1c or by glucose values. Diagnostic sensitivity of HbA1c appeared to be lower when compared with OGTT.

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