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

Arun Raghavan, Nanditha Arun, Snehalatha Chamukuttan, Priscilla Susairaj, Vijaya Lakshminarayanan and Ramachandran Ambady

India Diabetes Research Foundation and Dr. A. Ramachandran’s Diabetes Hospitals, Chennai, India

*Corresponding author: Dr. Ramachandran Ambady, President, India Diabetes Research Foundation and Chairman of Dr. A. Ramachandran’s Diabetes Hospitals 28, Marshalls Road, Egmore, Chennai – 600 008, India, Tel: +91 44 28582003; Fax: +91 44 42146652; E-mail: ramachandran@vsnl.com

Rec date: Jul 04, 2016; Acc date: Jul 21, 2016; Pub date: Jul 28, 2016

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; Glycosylated 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].
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 persistent 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) 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/m²), 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/m² 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.
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.

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.
Discussion

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%, $\chi^2 = 4.0, p=0.046$) and presence of higher WC was more among women in groups 2 and 3 (men 57.2%, women 84.4% ($\chi^2=10.9, p<0.0001$). Prevalence of dyslipidaemia and hypertension were similar among men and women.

Table 2: Prevalence of cardiometabolic abnormalities among the study 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 | 59 | 53.2 | 27 | 60.0 | 95 | 60.1 | 0.492 |
| Men ≥ 90 (cm) | 12 | 85.7 | 19 | 86.4 | 24 | 77.4 | 0.651 |
| Women ≥ 80 (cm) | 57 | 45.6 | 23 | 34.3 | 90 | 47.6 | 0.165 |
| Cholesterol ≥ 200 (mg/dl) | 60 | 48.0 | 28 | 41.8 | 96 | 50.8 | 0.447 |
| Triglycerides ≥ 150 (mg/dl) | 53 | 42.4 | 37 | 55.2 | 96 | 51.1 | 0.178 |
| HDL-Cholesterol ≤ 40 (mg/dl) | 99 | 79.2 | 50 | 74.6 | 145 | 77.1 | 0.756 |
| LDL-cholesterol ≥ 100 (mg/dl) | 75 | 68.4 | 16 | 57.1 | 124 | 80.5 | 0.010 |
| 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 - Glycosolated Haemoglobin

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.

Acknowledgements

We gratefully acknowledge the help rendered by S. Selvam, Mary Simon, C.K. Sathish Kumar and A. Catherin Seeli in the conduct of the studies. No funding was received for this study.

References

1. Bonora E, Tuomilehto J (2011) The pros and cons of diagnosing diabetes with A1C. Diabetes Care 34: S184-S190.
2. The International Expert Committee (2009) Report on the role of the A1c assay in the diagnosis of diabetes. Diabetes Care 32: 1327-1334.
3. American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. Diabetes Care 33: S62-S69.
4. World Health Organization Consultation (2011) Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Diabetes Res Clin Pract 93: 299-309.
5. Cowie CC, Rust KE, Byrd-Holt D, Gregg EW, Ford ES, et al. (2010) Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988-2006. Diabetes Care 33: 562-568.
6. Rathmann W, Kowall B, Tamayo T, Giani G, Holle R, et al. (2012) Hemoglobin A1c and glucose criteria identify different subjects as having type 2 diabetes in middle-aged and older populations: the KORA S4/F4 Study. Ann Med 44: 170-177.
7. Christensen DL, Witte DR, Kadukaj L, Jorgensen ME, Borch-Johnsen K, et al. (2010) Moving to an A1C-based diagnosis of diabetes has a different impact on prevalence in different ethnic groups. Diabetes Care 33: 580-582.
8. Lorenzo C, Haffner SM (2010) Performance characteristics of the new definition of diabetes: the insulin resistance atherosclerosis study. Diabetes Care 33: 335-337.
9. Olson DE, Rhee MK, Herrick K, Ziemer DC, Twombly JG, et al. (2010) Screening for diabetes and pre-diabetes with proposed A1C-based diagnostic criteria. Diabetes Care 33: 2184-2189.
10. Mostafa SA, Khunti K, Kilpatrick ES, Webb D, Srinivasan BT, et al. (2013) Diagnostic performance of using one- or two-HbA1c cut-point strategies to detect undiagnosed type 2 diabetes and impaired glucose regulation within a multi-ethnic population. Diab Vasc Dis Res 10: 84-92.
11. Vlaar EM, Amirab WM, Busschers WB, Hollemen F, Nierkens V, et al. (2013) Screening South Asians for type 2 diabetes and prediabetes: (1) comparing oral glucose tolerance and haemoglobin A1c test results and (2) comparing the two sets of metabolic profiles of individuals diagnosed with these two tests. BMC Endocr Disord 13: 8.
12. Borg R, Vitsinen D, Witte DR, Borch-Johnsen K (2010) Comparing risk profiles of individuals diagnosed with diabetes by OGTT and HbA1c The Danish Inter99 study. Diabet Med 27: 906-910.
13. Boronat M, Saavedra P, Lopez-Rios L, Riano M, Wagner AM, et al. (2010) Differences in cardiovascular risk profile of diabetic subjects discordantly classified by diagnostic criteria based on glycated hemoglobin and oral glucose tolerance test. Diabetes Care 33: 2671-2673.
14. Xu N, Wu H, Li D, Wang J (2014) Diagnostic accuracy of glycated hemoglobin compared with oral glucose tolerance test for diagnosing diabetes mellitus in Chinese adults: A meta-analysis. Diabetes Res Clin Pract 106: 11-18.
15. Zhou X, Pang Z, Gao W, Wang S, Zhang L, et al. (2010) Performance of an A1C and fasting capillary blood glucose test for screening newly diagnosed diabetes and pre-diabetes defined by an oral glucose tolerance test in Qingdao, China. Diabetes Care 33: 545-550.
16. Borch-Johnsen K, Tuomilehto J, Balkau B (1998) Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. Br Med J 317: 371-375.
17. Ramachandran A, Snehalatha C, Shetty AS, Nanditha A (2011) Predictive value of HbA1c for incident diabetes among subjects with impaired glucose tolerance—a meta-analysis of the Indian Diabetes Prevention Programmes. Diabet Med 29: 94-98.
18. Mohan V, Vijayachandrika V, Gokulakrishnan K, Anjana RM, Ganesan A, et al. (2010) A1C cut points to define various glucose intolerance groups in Asian Indians. Diabetes Care 33: 515-519.
19. McCance DR, Hanson RL, Charles MA, Jacobsson LT, Pettitt DJ, et al. (1994) Comparison of tests for glycosylated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ 308: 1323-1328.
20. World Health Organization (1999) Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation, Part 1: Diagnosis and Classification of Diabetes Mellitus, World Health Organization, Geneva.
21. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, et al. (2006) The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDDP-1). Diabetologia 49: 289-297.
22. Ramachandran A, Snehalatha C, Mary S, Selvam S, Kumar CK, et al. (2009) Pioglitazone does not enhance effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results from the Indian Diabetes Prevention Programme-2 (IDPP-2). Diabetesologia 52: 1019-1026.
23. Snehalatha C, Satyavani K, Sivasankari S, Vijay V, Ramachandran A (1999) Insulin secretion and action in different stages of glucose tolerance in Asian Indians. Diabet Med 16: 408-414.
24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, et al. (1985) Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412-419.
25. Sacks DB (2011) A1c versus glucose testing: A comparison. Diabetes Care 34: 518-523.
26. Wisdom K, Fryzek JP, Havstad SL, Anderson RM, Dreiling MC, et al. (1997) Comparison of laboratory test frequency and test results between African-Americans and Caucasians with diabetes: opportunity for improvement. Findings from a large urban health maintenance organization. Diabetes Care 20: 971-977.
27. Peng G, Lin M, Zhang K, Chen J, Wang Y, et al. (2013) Hemoglobin A1c can identify more cardiovascular and metabolic risk profile in OGTT-negative Chinese population. Int J Med Sci 10: 1028-1034.
28. Zhang YH, Ma WJ, Thomas GN, Xu YJ, Lao XQ, et al. (2012) Diabetes and pre-diabetes as determined by glycated haemoglobin a1c and glucose levels in a developing southern Chinese population. PLoS one 7:e37260.
29. Kim CH, Kim HK, Bae SJ, Park JY, Lee KU (2011) Discordance between fasting glucose-based and hemoglobin A1c-based diagnosis of diabetes mellitus in Koreans. Diabetes Res Clin Pract 91: e8-e10.
30. Ramachandran A, Snehalatha C (2010) Rising burden of obesity in Asia. J Obes pii: 868573.