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RESEARCH ARTICLE

Baseline level of 30-min plasma glucose is an independent predictor of incident diabetes among Asian Indians: analysis of two diabetes prevention programmes

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Abstract

Background The objective was to study the ability of the 30-min plasma glucose (30-min PG) during an oral glucose tolerance test to predict the future risk of type 2 diabetes among Asian Indians with impaired glucose tolerance.

Methods For the present analyses, we utilized data from 753 participants from two diabetes primary prevention studies, having complete data at the end of the study periods, including 236 from Indian Diabetes Prevention Programme-1 and 517 from the 2013 study. Baseline 30-min PG values were divided into tertiles: T1 $<$ 9.1 mmol/L ($<$163.0 mg/dL); T2 9.2–10.4 mmol/L (164.0–187.0 mg/dL) and T3 $\geq$ 10.4 mmol/L ($\geq$188 mg/dL). The predictive values of tertiles of 30-min PG for incident diabetes were assessed using Cox regression analyses

Results At the end of the studies, 230 (30.5%) participants developed diabetes. Participants with higher levels of 30-min PG were more likely to have increased fasting, 2-h PG and HbA_{1c} levels, increased prevalence of impaired fasting glucose and decreased beta cell function. The progression rate of diabetes increased with increasing tertiles of 30-min PG. Cox's regression analysis showed that 30-min PG was an independent predictor of incident diabetes after adjustment for an array of covariates [Hazard Ratio (HR):1.44 (1.01–2.06)]

Conclusions This prospective analysis demonstrates, for the first time, an independent association between an elevated 30-min PG level and incident diabetes among Asian Indians with impaired glucose tolerance. Predictive utility of glycemic thresholds at various time points other than the traditional fasting and 2-h PG values should therefore merit further consideration. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords incidence of diabetes; 30-min plasma glucose; Asian Indian; type 2 diabetes; impaired glucose tolerance; oral glucose tolerance test

Abbreviations BMI, body mass index; IDPP, Indian Diabetes Prevention Programme; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose; T2DM, type 2 diabetes

Introduction

Prediabetes, defined as blood glucose concentrations higher than normal but lower than diabetes thresholds, is a high-risk state for the development of type 2 diabetes (T2DM) [1]. Categories of prediabetes include impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), both of which can appear in isolation or in combination (combined glucose intolerance; IFG + IGT) [2]. The 75-g oral glucose tolerance test (OGTT) has traditionally been used as a standard procedure to identify IFG and IGT. However, plasma glucose values at either 30-min plasma glucose (30-min PG) and/or at 60 min intervals are not considered very important in a clinical setting. There is ample evidence available to show that glycemic measurements at interim intervals are strong predictors of T2DM and its associated complications compared with conventional glycemic measures [3–9]. Furthermore, measurements taken at these time points provide additional information regarding insulin sensitivity and beta cell function [10,11]. Most studies assessing the pathogenesis of diabetes have been conducted in Caucasian and European populations. Information is sparse on the utility of 30-min PG in predicting the progression to T2DM among Asian Indians. Therefore, the primary objective of this analysis was to assess the ability of the 30-min PG during an OGTT to predict the future risk of T2DM in this population with IGT.

Materials and methods

Data from two Indian Diabetes Prevention Programmes [12,13] were pooled for this ancillary analysis. Figure 1 shows the selection of the participants for this analysis. The number in the control and intervention arms and the incidence of diabetes in the studies are shown in Figure 1. The Indian Diabetes Prevention Programme-1 (IDPP-1) [12] was a 3-year prospective randomized controlled trial in participants with IGT. The primary cohort consisted of 531 (421 men and 110 women) from 35 to 55 years of age. They were randomized into four study groups: group 1 received standard advice (control; $n = 136$) at baseline; group 2 received moderate lifestyle advice regularly ($n = 133$); group 3 was treated with metformin (500 mg/day; $n = 133$) and group 4 was treated with both lifestyle intervention and metformin (500 mg/day; $n = 129$). This study showed that both lifestyle intervention and metformin were equally effective (relative risk reduction, 28.5% and 26.4%, respectively) in preventing diabetes in this high-risk Asian Indian population.

The second study, completed in 2013, examined the effect of a mobile phone-based lifestyle intervention, delivered via text messages [13]. A total of 537 high-risk men were randomized into two groups: a control group that received standard lifestyle advice only at baseline and an intervention group that, in addition to the baseline standard care advice, received tailored text messages pertaining to healthy lifestyle habits over a 2-year period. Among them, 517 participants completed the 2-year follow-up. The study showed for the first time that healthy reminders through text messaging is an effective and acceptable tool to deliver and support lifestyle modification to prevent T2DM in Asian Indian men with IGT (relative risk reduction: 36.0%).

For the present analyses, we utilized data from 753 participants having complete data at the end of the study periods, including 236 from IDPP-1 and 517 from the 2013 study (Figure 1). For this analysis, we selected those who had baseline and follow-up details of anthropometry, glycaemic outcome and values for homeostasis model assessment-insulin resistance (HOMA-IR) and beta cell function. Height, weight [body mass index (BMI) calculated] and waist circumference were measured using standard procedures. At 6 and 18 months' visits, a 2-h post-glucose load test was performed. If this value was $\geq 11 \cdot 1$ mmol/L (200 mg/dL), a three-sample OGTT was performed within a week with venous plasma sampling in the fasting state and at 30 and 120 min after a glucose load. At annual visits, we performed OGTT for all non-diabetic individuals. The primary outcome was a development of diabetes as classified by the World Health Organization recommendations [14]: a fasting plasma glucose $\geq 7 \cdot 0$ mmol/L (126 mg/dL) and/or a 2-h post-glucose value $\geq 11 \cdot 1$ mmol/L (200 mg/dL). Plasma glucose was measured by the glucokinase method in IDPP-1 and hexokinase method in the 2013 study. Total lipid profile was measured using the automated enzymatic assays (Roche diagnostics, Mannheim, Germany). Plasma insulin was measured using the Radio-Immuno Assay Kit (Diasorin, Saluggia, Italy; sensitivity of <24 pmol/L and intraassay and interassay coefficient of variations (CVs) of $<10\%$) in IDPP-1 and by electro chemiluminescence assay (ElesysCobas e411 auto-analyser; Roche diagnostics, Mannheim, Germany; CV $<3\%$; detection range: 1.39–6945 pmol/L) in 2013 study. Although the methodologies for plasma glucose and plasma insulin estimations were different, the respective pairs of tests were strongly correlated. Insulin resistance [15] was calculated using the formula: HOMA-IR:([fasting insulin (mU/l) $\times$ fasting glucose (mmol/l)]/$22 \cdot 5$). Beta cell function was calculated using the formula: total area under curve insulin / glucose (AUCI / G) * Matsuda's insulin sensitivity index [16].

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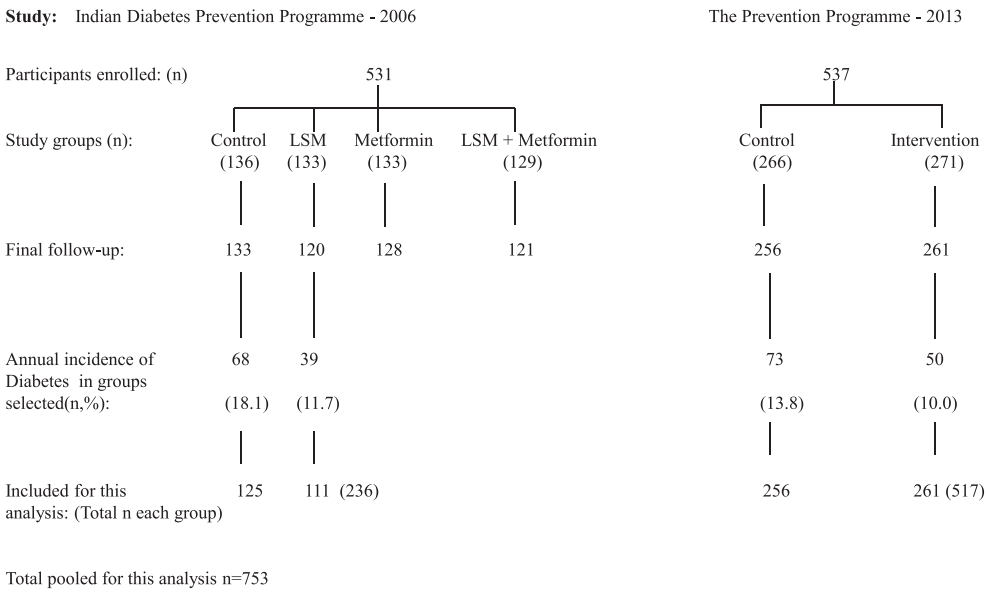

Figure 1. Flow diagram showing the selection criteria of participants for the analysis

Statistical analysis

Thirty-minute PG during the OGTT was divided into tertiles for this analysis: T1 <9.1 mmol/L (<163.0 mg/dL); T2 9.2–10.4 mmol/L (164.0–187.0 mg/dL) and T3 ≥10.4 mmol/L (≥188 mg/dL). Comparisons between groups were performed using the χ^2 test for qualitative variables, one-way analysis of variance for the normally distributed variables and the non-parametric Kruskal–Wallis test for skewed distributions. The prediction of tertiles of 30-min PG with diabetes was assessed using Cox regression analysis in four models: (1) unadjusted model, (2) model-1 adjusted for study group (control *vs* intervention), baseline age and BMI, (3) model-2 adjusted for model-1 + fasting plasma glucose and HbA_{1c} and (4) model-3 adjusted for model-2 + 120-min PG. All analyses were performed using IBM SPSS 19.0 software (IBM Corp., Armonk, NY).

Results

Among the 753 participants included in the analysis, 230 (30.5%) progressed to diabetes. Table 1 shows the baseline characteristics by tertiles of 30-min PG levels. Participants with higher levels of plasma 30-min PG values were likely to have increased fasting, 2-h plasma glucose (2-h PG) and HbA_{1c} levels, increased prevalence of IFG and decreased beta cell function.

The incident rate of diabetes increased with increasing tertiles of 30-min PG [T1: 62 (24.2%); T2: 71 (28.5%); T3: 97 (39.1%); $P = 0.001$]. The hazard ratios of developing diabetes by tertiles of 30-min PG using those in the lowest third as the reference group are shown in Table 2. The levels were independently predictive of T2DM even after adjustment for age, study group (intervention *vs* control), BMI, fasting plasma glucose and HbA_{1c} [1.52 (1.07–2.11)]. Further adjustment for 2-h PG, although still significant, attenuated the relationship between 30-min PG and diabetes [1.44 (1.01–2.06); Table 2]. Disposition index was not included in this model as surrogate measures for calculating beta cell function encompassed all the glycemic measures.

Discussion

This prospective analysis demonstrates for the first time the existence of independent association between elevated 30-min PG level and incident diabetes among Asian Indians with IGT at baseline. The association remained significant even after adjusting for fasting and 2-h PG levels and HbA_{1c}. In a large cohort of 1611 participants in a Scandinavian population followed for 7–8 years, Ghani *et al.* [3] reported that both increased 30-min PG and 1-h PG measurements were better predictors of future diabetes than fasting glucose. The addition of 1-h PG to the existing fasting-based risk scores such as the San Antonio diabetes prediction model and Adult Treatment Panel III further improved predictive utility for identifying high-risk individuals. Additionally, a 33-year prospective study of a large Israeli cohort found that 2-h PG levels changed minimally, whereas 1-h PG levels increased incrementally across HbA_{1c} quintiles suggesting

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Table 1. Baseline characteristics of study participants stratified based on 30-min plasma glucose (in tertiles)

Variables	Over all $n = 753$	Tertile-1 $n = 256$	Tertile-2 $n = 249$	Tertile-3 $n = 248$	P value [1]
Age (years)	45.9 ± 5.0	45.7 ± 4.8	46.6 ± 5.1	45.6 ± 5.1	0.043
Body mass index (kg/m^2)	25.9 ± 3.3	26.0 ± 3.4	25.8 ± 3.1	25.9 ± 3.2	0.645
Waist circumference (cm)	91.5 ± 7.8	91.8 ± 8.8	91.5 ± 7.4	91.3 ± 7.1	0.773
Blood pressure (mmHg)					
Systolic	123.0 ± 4.3	122.1 ± 14.8	122.9 ± 12.3	124.2 ± 15.5	0.298
Diastolic	78.7 ± 8.7	78.3 ± 9.1	79.0 ± 8.5	78.8 ± 8.5	0.745
Plasma glucose (mmol/L)					
Fasting	5.6 ± 0.6	5.3 ± 0.6	5.6 ± 0.5	5.9 ± 0.6	<0.0001
2 h	8.7 ± 0.8	8.6 ± 0.7	8.8 ± 0.8	8.8 ± 0.9	<0.0001
Baseline IFG (n, %)	147 (19.5)	19 (7.4)	39 (15.7)	89 (35.7)	<0.0001
HbA_{1c} (%) (mmol/mol)	6.2 ± 0.4 (44)	6.0 ± 0.4 (42)	6.1 ± 0.4 (43)	6.3 ± 0.4 (45)	<0.0001
Lipid profile (mmol/L)					
Triglycerides[2]	1.6 (1.2–2.1)	1.6 (1.2–2.1)	1.6 (1.2–2.1)	1.6 (1.1–2.2)	0.658
Cholesterol	4.9 ± 0.9	4.9 ± 0.9	4.9 ± 0.8	4.9 ± 0.9	0.937
HDL-cholesterol	0.9 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.323
HOMA-IR	3.8 ± 2.1	3.7 ± 2.3	3.6 ± 1.9	3.9 ± 2.1	0.181
Beta cell function[2]	145.4 (113.5–184.2)	192.0 (152.2–241.6)	163.1 (132.9–196.7)	126.6 (100.9–163.7)	<0.0001

Plasma levels of 30-min OGTT-derived glucose are divided into tertiles for this analysis: T1 (<163.0 mg/dL); T2 (164.0–187.0 mg/dL) and T3 (≥188 mg/dL).
[1]Data are expressed as mean ± SD for normally distributed variables and analysed using one-way ANOVA, as counts (percentages) for qualitative variables and analysed by χ^2 test.
[2]Triglycerides and beta cell function are expressed as median (IQR) for non-normally distributed variables and analysed using the Kruskal–Wallis test.
IFG, impaired fasting glucose; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; OGTT, oral glucose tolerance test; SD, standard deviation; ANOVA, analysis of variance.

Table 2. Cox's regression model showing the predictive power of 30-min plasma glucose

Variables	Tertile-1	Tertile-2	Tertile-3
Incidence of diabetes (n, %)	62 (24.2)	71 (28.5)	97 (39.1)
		HR [95% confidence interval]	
Unadjusted	Reference	1.37 [0.97–1.92]	1.89 [1.37–2.59]
Model 1: adjusted for age, intervention group, BMI	Reference	1.35 [0.96–1.90]	1.90 [1.38–2.61]
Model 2: model 1 further adjusted for fasting plasma glucose and HbA_{1c}	Reference	1.25 [0.88–1.77]	1.52 [1.07–2.11]
Model 3: Model 2 further adjusted for 120-min plasma glucose	Reference	1.22 [0.86–1.73]	1.44 [1.01–2.06]

Dependent variable: diabetes *versus* others.
BMI, body mass index.

that the 1-h PG level may identify participants at high risk [5]. A hospital-based observational study among 1179 Asian Indian individuals showed that the 1-h PG≥155 mg/dL had increased risk of developing prediabetes and T2DM over 13 years of follow-up period [17]. The novelty of our findings are that (1) the samples were derived from randomized controlled settings, (2) participants had persistent prediabetes at baseline with compromised beta cell function and (3) the BMI was lower than in the western cohorts [3,4] (but elevated for the Asian Indian population). Therefore, our report further strengthens the utility of early glucose measurements (30 min or 1 h) during OGTT as an independent predictor of future risk of T2DM.

In this cohort, the prevalence of combined glucose intolerance (IFG + IGT) was higher in participants with raised 30-min PG values. IFG is characterized by reduced early-phase insulin secretion, and therefore, the elevated 30-min PG is a surrogate marker of abnormal beta cell function. Previously, the European Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) study showed a stronger association between 1-hr PG levels with decreased insulin sensitivity and impaired beta cell function compared with the 2-hr PG value [10].

Identification of the prediabetic stage (IGT and IFG) has been used to identify individuals with high risk for T2DM. Indeed, all the major landmark primary prevention studies in T2DM have recruited individuals with IGT for assessing

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the benefits of intervention strategies [12,13,18]. However, longitudinal studies have demonstrated that more than one-third of individuals who develop T2DM have normoglycemia at the time of recruitment [19]. Therefore, prediabetes categories based on fasting and 2-h PG as the sole means of identifying individuals at high risk for T2DM may overlook a considerable proportion of individuals who will develop T2DM over time [19]. In this cohort, although all the participants had IGT at baseline, 154 (19.9%) individuals had 30-min PG in the diabetic range (≥200 mg/dL; 11.1 mmol/L). The ancillary analysis showed that the likelihood of developing diabetes is higher in individuals with 30-min PG ≥11.1 mmol/L than in non-diabetic range [30-min PG <11.1 mmol/L: 166 (27.7%) *vs* 30-min PG ≥11.1 mmol/L: 64 (41.6%); $P = 0.001$]. The peak glucose absorption occurs mostly 30–60 min after ingesting a mixed meal and therefore potentially represents an optimal period to detect the earliest evidence of metabolic dysfunction [20].

In clinical practice, neither IFG nor IGT is considered clinical entities *per se* but rather risk categories for development of T2DM and cardiovascular diseases. Large-scale prospective analysis of alternative novel glycemic markers derived from OGTT such as 30-min PG or 1-h PG is warranted. Confirmatory results would suggest that the 2-h time point during the OGTT could be replaced with the 30-min or 1-h post-load value that will avoid the disadvantages of doing a 2-h test and also enable early referral of the high-risk persons for appropriate preventive intervention. A simplified OGTT procedure would likely encourage greater utilization and hence identify a large proportion of individuals with IGT and/or IFG + IGT who have high risk for development of T2DM. In summary, our data suggest that the 30-min PG may represent an index of metabolic impairment, useful in clinical practice to identify individuals at high risk of developing T2DM. Predictive utility of glycemic thresholds at various time points other than the traditional fasting and 2-h PG values should therefore be considered in clinical settings.

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Author contributions

Dr C. Snehalatha and Dr J. Ram have performed conceptualization of hypothesis, contributed to discussion, wrote manuscript and reviewed/edited manuscript. Dr. A. Nanditha, Dr. Samith A. Shetty and Dr. Mary Ann Sevick have contributed to discussion and reviewed/edited manuscript. Prof. Michael Bergman has performed conceptualization of hypothesis and reviewed/edited manuscript. Prof. D. G. Johnston has researched data, contributed to discussion and reviewed/edited manuscript. Prof. A. Ramachandran has performed conceptualization of hypothesis, contributed to discussion and reviewed/edited manuscript.

Conflicts of interest

None declared.

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