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One-hour and two-hour postload plasma glucose concentrations are comparable predictors of type 2 diabetes mellitus in Southwestern Native Americans

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Abstract

Aims/hypothesis Elevated 2-h plasma glucose concentration (2 h-PG) during a 75 g OGTT predict the development of type 2 diabetes mellitus. However, 1-h plasma glucose concentration (1 h-PG) is associated with insulin secretion and may be a better predictor of type 2 diabetes. We aimed to investigate the association between 1 h-PG and 2 h-PG using gold standard methods for measuring insulin secretion and action. We also compared 1 h-PG and 2 h-PG as predictors of type 2 diabetes mellitus.

Methods This analysis included adult volunteers without diabetes, predominantly Native Americans of Southwestern heritage, who were involved in a longitudinal epidemiological study from 1965 to 2007, with a baseline OGTT that included measurement of 1 h-PG. Group 1 ($n = 716$) underwent an IVGTT and hyperinsulinaemic–euglycaemic clamp for measurement of acute insulin response (AIR) and insulin-stimulated glucose disposal (M), respectively. Some members of Group 1 ($n = 490$ of 716) and members of a second, larger, group (Group 2; $n = 1946$) were followed-up to assess the development of type 2 diabetes (median 9.0 and 12.8 years follow-up, respectively).

Results Compared with 2 h-PG ($r = -0.281$), 1 h-PG ($r = -0.384$) was more closely associated with AIR, whereas, compared with 1 h-PG ($r = -0.340$), 2 h-PG ($r = -0.408$) was more closely associated with M . Measures of 1 h-PG and 2 h-PG had similar abilities to predict type 2 diabetes, which did not change when both were included in the model. A 1 h-PG cut-off of 9.3 mmol/l provided similar levels of sensitivity and specificity as a 2 h-PG cut-off of 7.8 mmol/l; the latter is used to define impaired glucose tolerance, a recognised predictor of type 2 diabetes mellitus.

Conclusions/interpretation The 1 h-PG was associated with important physiological predictors of type 2 diabetes and was as effective as 2 h-PG for predicting type 2 diabetes mellitus. The 1 h-PG is, therefore, an alternative method of identifying individuals with an elevated risk of type 2 diabetes mellitus.

Keywords 1-h plasma glucose · 2-h plasma glucose · Acute insulin response · Hyperinsulinaemic–euglycaemic clamp · OGTT · Prediction · Type 2 diabetes mellitus

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Abbreviations

AIR	Acute insulin response
FPG	Fasting plasma glucose
HIEC	Hyperinsulinaemic–euglycaemic clamp
1 h-PG	1-h plasma glucose concentration
2 h-PG	2-h plasma glucose concentration
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
M	Insulin-stimulated glucose disposal
NGT	Normal glucose tolerance
ROC	Receiver operating characteristic
SWNA	Southwestern Native American

Introduction

Accurate identification of individuals at an elevated risk of developing type 2 diabetes is important for prevention of both type 2 diabetes and its complications. Impaired glucose tolerance (IGT) based on the 2-h plasma glucose concentration (2 h-PG; i.e. ≥ 7.8 mmol/l and < 11.1 mmol/l) during the OGTT is a well-recognised indicator of elevated risk of future type 2 diabetes [1]. In contrast, the 1-h plasma glucose concentration (1 h-PG) is not used to identify those at elevated risk in the current ADA criteria [1]. Although the potential contribution of 1 h-PG was previously appreciated, as shown by inclusion of 1 h-PG in the 1979 National Diabetes Data Group criteria for classifying IGT [2], it was later deemed unnecessary in criteria set out by the WHO, which included 2 h-PG as the only post-challenge time point required for IGT classification [3, 4]. However, interest in 1 h-PG has recently re-emerged.

The San Antonio Heart Study reported that 1 h-PG had a greater area under the receiver operating characteristic (ROC) curve for predicting type 2 diabetes compared with 2 h-PG [5]. This was also demonstrated in the Botnia and Malmö Prevention Project cohorts [6, 7], and was attributed to closer association between 1 h-PG with insulin action and secretion [5]. Using insulin action as measured by the hyperinsulinaemic–euglycaemic clamp (HIEC) as the reference standard, correlation between 1 h-PG and insulin action was similar [8] or stronger [9] than that of 2 h-PG. Similar to the San Antonio Heart Study [5], others have found that 1 h-PG is more strongly associated with surrogate measures of insulin secretion based on the OGTT [8]. The acute insulin response (AIR) to the IVGTT [10] is a more accurate measure of insulin secretion. Using IVGTT, AIR was reduced in those with normal glucose tolerance (NGT) and high 1 h-PG (> 8.6 mmol/l) compared with those with normal NGT and low 1 h-PG [11]. However, whether the 1 h-PG was better associated with AIR, compared with glucose concentrations from other time points during the OGTT was not evaluated.

Besides using 1 h-PG as a single predictor, combining 1 h-PG and 2 h-PG may be useful for further risk stratification. Of individuals with IGT and NGT (as defined by 2 h-PG), those with elevated 1 h-PG (i.e. ≥ 8.6 mmol/l) are at greater risk of type 2 diabetes [12] and mortality [13] compared with those with low 1 h-PG. Moreover, in recent studies, those with NGT and 1 h-PG above 8.6 mmol/l had greater subclinical inflammation [14], greater carotid intima–media thickness [15], worse echocardiographic markers of diastolic dysfunction [16] and lower eGFR [17], further suggesting that 1 h-PG during OGTT is potentially useful.

To clarify how 1 h-PG compares with 2 h-PG in its associations with important predictors of type 2 diabetes, we investigated the association of 1 h-PG and 2 h-PG with AIR by IVGTT, and insulin-stimulated glucose disposal (*M*) using the

HIEC, both of which are reference methods for the measurement of insulin secretion and action, respectively [18]. In Group 1, participants were Native Americans without type 2 diabetes at baseline ($n = 716$). To compare the predictive value of 1 h-PG and 2 h-PG, we then looked at development of type 2 diabetes in a subset of Group 1 ($n = 490$ of 716). In a second, larger, group (Group 2; $n = 1946$) of adults, also of Native American ancestry, we compared the abilities of 1 h-PG and 2 h-PG to predict future type 2 diabetes individually and in combined models.

Methods

Study population

A subset of participants in a longitudinal epidemiological study conducted in a Southwestern Native American (SWNA) community in Arizona, USA, were included in this study [19]. In this longitudinal study, which began in 1965 and ended in 2007, individuals aged 5 years and over were invited for outpatient research examinations approximately every 2 years. These examinations included an OGTT, consisting of venous plasma glucose measurements at 1- and 2-h post-glucose load (1 h-PG measurement was done prior to 1980 but not after) [19].

Adult community members without type 2 diabetes were also invited to participate in an inpatient metabolic study to assess determinants of type 2 diabetes, as previously described [20]. These participants were admitted to the Clinical Research Unit in Phoenix, AZ, USA, and were determined to be otherwise healthy based on a complete medical history and physical examination, including routine laboratory tests, and were not taking medications known to affect glucose or insulin metabolism 1 month prior to baseline measurements. After admission, volunteers were fed a weight-maintaining diet (energy distribution: 50% carbohydrates, 30% fat, 20% protein) and abstained from strenuous activity. After at least 3 days of weight-maintaining diet, a series of tests were conducted including an OGTT (which routinely involved 1 h-PG), evaluation of body composition, HIEC and IVGTT.

Group 1 In Group 1 of the present study, we included only non-pregnant adults (age ≥ 18 years) without type 2 diabetes at baseline (inpatient visits between 1982 and 2007). All of these participants were also part of the outpatient longitudinal study. To evaluate the association between 1 h-PG and 2 h-PG with *M* and AIR, the study visit at which the first HIEC and IVGTT results were available was used for cross-sectional analysis (Group 1, $n = 716$); 490 of the 716 group members had follow-up for development of type 2 diabetes (Table 1).

Table 1 Baseline characteristics

Variables	Group 1		Group 2
	Cross-sectional	Longitudinal	Longitudinal
<i>n</i>	716	490	1946
Male (%)	58.4	57.1	41.8
Age (years) ^a	26.7 (22.6, 32.6)	26.0 (22.3, 31.6)	25.4 (20.0, 37.9)
BMI (kg/m ²) ^b	33.7 (8.1)	33.8 (7.4)	30.0 (6.5)
Body fat (%) ^b	31.7 (8.9)	32.7 (8.3)	–
FPG (mmol/l) ^b	4.96 (0.55)	4.96 (0.55)	5.07 (0.57) ^l
1 h-PG (mmol/l) ^b	8.25 (2.00)	8.18 (1.98)	7.05 (2.21)
2 h-PG (mmol/l) ^b	6.72 (1.71)	6.77 (1.71)	6.15 (1.60)
NGT, <i>n</i> (%)	477 (66.6)	325 (66.3)	1649 (84.7) ^p
IGT, <i>n</i> (%)	137 (19.1)	97 (19.8)	297 (15.3) ^p
IFG, <i>n</i> (%)	40 (5.6)	26 (5.3)	–
IGT + IFG, <i>n</i> (%)	62 (8.7)	42 (8.6)	–
Fasting insulin (pmol/l) ^a	236.1 (158.3, 349.9) ^d	253.1 (173.6, 368.1) ^h	145.8 (97.2, 215.3) ^m
Total cholesterol (mmol/l) ^b	4.49 (1.06) ^c	4.43 (0.92) ⁱ	4.55 (0.94) ⁿ
Serum creatinine (μmol/l) ^a	79.6 (70.7, 97.2) ^f	70.7 (61.9, 88.4) ^j	66.3 (57.5, 76.0) ⁿ
Systolic BP (mmHg) ^b	125 (14) ^g	124 (15) ^k	128 (20) ^o
Diastolic BP (mmHg) ^b	80 (13) ^g	80 (13) ^k	77 (12) ^o
Native American, <i>n</i> (%)	716 (100)	490 (100)	1946 (100)
SWNA heritage, <i>n</i> (%)	433 (60.5)	375 (76.5)	1515 (77.9)
<i>M</i> (μmol kg _{EMBS} ⁻¹ min ⁻¹) ^c	15.0 (14.4, 15.4)	14.1 (13.7, 14.6)	–
AIR (pmol/l) ^c	1192 (1131, 1256)	1398 (1322, 1479)	–
Follow-up (years) ^a	–	9.0 (5.5, 12.7)	12.8 (6.1, 22.4)
Type 2 diabetes events, <i>n</i> (%)	–	164 (33)	1010 (52)

^a Data are reported as the median (IQR; 25th to 75th percentile)^b Data are reported as the mean (SD)^c Data are reported as the geometric mean (95% CI)^d *n* = 703; ^e *n* = 545; ^f *n* = 564; ^g *n* = 602; ^h *n* = 481; ⁱ *n* = 376; ^j *n* = 374; ^k *n* = 426; ^l *n* = 458; ^m *n* = 420; ⁿ *n* = 1499;^o *n* = 1506^p Classification is based on 2 h-PG only

EMBS, estimated metabolic body size

Group 2 We further evaluated 1 h-PG and 2 h-PG as predictors of type 2 diabetes in participants in a second, larger, group (Group 2, *n* = 1946; Table 1) who had both baseline 1 h-PG and 2 h-PG data available (all participants in this group were examined prior to 1980, in the longitudinal study; baseline visits were between 1966 and 1979). Additional analysis involving Group 2 was conducted to confirm the findings in Group 1. Participants in Group 2 generally had longer follow-up time than those in Group 1 and the majority did not participate in the inpatient study. Among those in Group 2, 108 individuals (6%) were also included in Group 1, although the baseline visits were completed at different times. Compared with the healthy Group 1 volunteers, individuals with medical conditions (e.g. cardiovascular, neurological, rheumatological, infectious diseases), except for pregnancy, were not specifically excluded from Group 2.

Classification of type 2 diabetes was based on the 2003 ADA criteria [21]. The date of diagnosis was determined from research examinations or from a review of clinical records if type 2 diabetes was diagnosed during routine medical care. Written informed consent was obtained from all participants. Both studies were approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases.

OGTT

All volunteers underwent a 75 g OGTT with venous plasma glucose measurements. For those who participated in the inpatient study, the OGTT was performed after an overnight fast and glucose levels were measured at fasting (0 h) and after 0.5, 1, 2 and 3 h. Individuals with both 1 h-PG and 2 h-PG data had

undergone OGTTs at outpatient visits, prior to 1980 [19], after which 1 h-PG data were not collected; participants were not routinely fasted prior to tests until 1975 and thereafter.

Body composition

Body composition was assessed by underwater weighing with simultaneous determination of residual lung volume by helium dilution [22] or by total body dual energy x-ray absorptiometry (DPX-L; Lunar Radiation, Madison, WI, USA). Absorptiometry measures were converged to comparable underwater weighing values, using a previously derived equation [23] to calculate percentage body fat.

HIEC

Insulin action was measured using a HIEC. As previously described [24], the procedure was performed after an overnight fast, whereupon a primed, continuous i.v. insulin infusion (40 mU/m², body surface area; Novo Nordisk, Bethesda, MD, USA) was administered for 100 min and a 20% dextrose solution was infused at various rates to maintain a plasma glucose of 5.6 mmol/l. *M*, the total insulin-stimulated glucose disposal, was determined from the last 40 min of the insulin infusions, while correcting for the steady-state insulin plasma concentration and endogenous glucose output. Only HIECs with a CV of >5% for glucose concentrations in the last 40 min of the insulin infusion were included in the analysis. Endogenous glucose output was measured via primed [3-³H] glucose (prepared at the Clinical Center Department of Nuclear Medicine of the National Institutes of Health, Bethesda, MD, USA) infusions. *M* was normalised by using estimated metabolic body size (fat-free mass + 17.7 kg) [25].

IVGTT

A 25 g i.v. glucose bolus injection was administered over 3 min for measurement of insulin secretion [26, 27]. AIR was calculated as the mean of the 3, 4 and 5 min IVGTT insulin concentrations minus the fasting concentration [27].

Analytical procedures

Plasma glucose was measured by either the modified Hoffman method (Technicon Instruments, Tarrytown, NY, USA) or the glucose oxidase method (Beckman Instruments, Fullerton, CA, USA). Plasma insulin concentrations were determined by the Herbert modification [28] of the Yalow and Berson method [29] or by automated analysers (Access, Beckman Instruments; Concept 4, ICN Radiochemicals, Costa Mesa, CA, USA). Values from the final later insulin assays were regressed to those of the original assay.

Statistical analysis

Statistical analyses were performed using SAS (Version 9.4, Cary, NC, USA). *M* and AIR were non-normally distributed data and were log₁₀-transformed. Pearson correlation coefficients were determined for normally distributed variables to evaluate bivariate associations between continuous data, while Spearman correlation coefficients were used for data which remained skewed despite log₁₀ transformation. Steiger's Z test was used to compare correlation coefficients [30, 31]. The cumulative incidence of type 2 diabetes was estimated using the Kaplan–Meier method [32]. To evaluate 1 h-PG and 2 h-PG as predictors of type 2 diabetes in Groups 1 and 2, proportional hazard analysis was used to calculate HRs for development of type 2 diabetes, adjusting for baseline age, sex, BMI and SWNA heritage status. The fraction of SWNA heritage (in eighths, ranging from 0/8 to 8/8) was determined from personal history and family data, as previously described [33]. For this study, SWNA heritage was considered a dichotomous variable (those with 8/8 SWNA heritage vs those less than 8/8 SWNA heritage). Proportional hazards assumptions were checked by assessment of plots of (1) log(−log[survival]) vs log of survival time and (2) Schoenfeld's residual against time. To facilitate comparisons, continuous variables including 1 h-PG and 2 h-PG were standardised (i.e. mean = 0, SD = 1) and the HR was reported per SD.

Since proportional hazards models including both 1 h-PG and 2 h-PG are difficult to interpret because of collinearity, prediction models for type 2 diabetes (accounting for time-to-event and enabling calculation of C-statistics) were created to compare the predictive abilities of 1 h-PG alone, 2 h-PG alone, and both 1 h-PG and 2 h-PG together. C-statistics permit a global measure of model discrimination, range from 0.5 to 1.0 (random to perfect concordance) and are analogous to the area under the ROC curve. In this context, the C-statistic represents the probability that given two randomly selected individuals, where one will develop type 2 diabetes prior to a specific follow-up time and the other who will not, the model will generate a higher risk score for the first individual than for the second individual [34]. C-statistics were calculated using the Pencina method [35] and compared using the DeLong method [36]. Unadjusted models including glucose from the OGTT were developed, and additional models were adjusted for known predictors of type 2 diabetes (age, sex, BMI and SWNA heritage). For graphical presentation, ROC curves were created for 1 h-PG and 2 h-PG based on the predicted cumulative incidence at 5 years and 25 years [37]. The cumulative incidence rate used for these analyses was calculated from the baseline hazard (Kaplan–Meier) function and the HR. A *p* value of <0.05 was considered statistically significant; correction for multiple testing was not carried out since hypotheses tested in this study have some support from the literature.

Results

Baseline characteristics of all participants are listed in Table 1. Characteristics at follow-up are reported in electronic supplementary material (ESM) Table 1. In Group 1, plasma glucose concentrations at all time points during the OGTT (0, 0.5, 1, 2 and 3 h) inversely correlated with *M* and AIR (adjusted for *M*; Table 2). The 2 h-PG had the highest correlation coefficient with *M* ($r = -0.408$, $p < 0.001$). Compared with 1 h-PG ($r = -0.340$, $p < 0.001$), 2 h-PG correlated more strongly with *M* (Steiger's *Z* test, $p < 0.02$). However, 1 h-PG ($r = -0.384$, $p < 0.001$) correlated more strongly with AIR (adjusted for *M*; Steiger's *Z* test, $p < 0.001$) compared with 2 h-PG ($r = -0.281$, $p < 0.001$). Results for AIR were consistent in subgroups with NGT and IGT, and the subgroup of individuals who identified as full SWNA heritage (i.e. 8/8): 1 h-PG remained more strongly correlated with AIR compared with 2 h-PG. When AIR was adjusted for age, sex, BMI and SWNA heritage, 1 h-PG still correlated more strongly with AIR compared with 2 h-PG ($r = -0.269$ and $r = -0.191$ for 1 h-PG and 2 h-PG, respectively, Steiger's *Z* test, $p < 0.01$; ESM Table 2).

Of the 716 volunteers in the cross-sectional analysis (Group 1), 490 (68%) were followed up for a median of 9.0 years (interquartile range [IQR], 5.5–12.7 years). Of the 490 participants with follow-up data, 325 (66%) had NGT, 26 (5%) had impaired fasting glucose (IFG), 97 (20%) had IGT and 42 (9%) had IFG plus IGT. A total of 164 of the 490 participants (33%) developed type 2 diabetes (Table 1). The percentages of participants with NGT, IGT, IFG and IFG plus IGT who converted to type 2 diabetes were 22%, 44%, 73% and 74%, respectively. In the subgroup with follow-up data, the correlation of *M* with 2 h-PG ($r = -0.355$, $p < 0.001$) and 1 h-PG ($r = -0.354$, $p < 0.001$) was similar, while AIR (adjusted for *M*) still correlated more strongly (Steiger's *Z* test, $p < 0.01$) with 1 h-PG ($r = -0.377$, $p < 0.001$) than with 2 h-PG ($r = -0.286$, $p < 0.001$) at baseline. In separate proportional hazards models adjusted for covariates (age, sex, BMI and SWNA heritage), 1 h-PG (HR 1.68 [95% CI 1.43, 1.97]; $p < 0.001$) and 2 h-PG (HR 1.98 [95% CI 1.66, 2.37]; $p < 0.001$) significantly predicted type 2 diabetes. In a model

including both 1 h-PG and 2 h-PG adjusted for covariates, 1 h-PG (HR 1.27 [95% CI 1.05, 1.58]; $p = 0.02$) and 2 h-PG (HR 1.69 [95% CI 1.36, 2.11]; $p < 0.001$) remained significant independent predictors of type 2 diabetes.

Proportional hazards models similar to those for Group 1 were also evaluated for 1946 participants in Group 2 (Table 1) who were followed up to monitor the development of type 2 diabetes for a median of 12.8 years (IQR, 6.1–22.4 years): 1010 participants developed type 2 diabetes. NGT and IGT converted to type 2 diabetes in 48% and 73% of participants, respectively. In separate models, each adjusted for covariates (age, sex, BMI and SWNA heritage), 1 h-PG (HR 1.71 [95% CI 1.60, 1.82]; $p < 0.001$) and 2 h-PG (HR 1.62 [95% CI 1.52, 1.74]; $p < 0.001$) were significantly associated with a risk of type 2 diabetes. When the proportional hazards model (adjusting for covariates) included both 1 h-PG and 2 h-PG, 1 h-PG (HR 1.46 [95% CI 1.34, 1.59]; $p < 0.001$) and 2 h-PG (HR 1.27 [95% CI 1.17, 1.39]; $p < 0.001$) were independently associated with a risk of type 2 diabetes. However, 1 h-PG and 2 h-PG correlated moderately to strongly with each other in Group 1 ($r = 0.658$, $p < 0.001$) and Group 2 ($r = 0.656$, $p < 0.001$), so the HR in the model including both 1 h-PG and 2 h-PG is difficult to interpret.

Because there was strong correlation among plasma glucose variables, risk prediction models accounting for time-to-event and providing a C-statistic describing a global measure of model discrimination were developed (ESM Tables 3–5) [34]. For Group 1, in models adjusting for the same covariates used in the proportional hazard models, 1 h-PG (C-statistic 0.744 [95% CI 0.708, 0.780]) was not significantly different from 2 h-PG (C-statistic 0.750 [95% CI 0.713, 0.787]; $p = 0.64$) when used as the only glucose time point (ESM Table 3). For Group 2, in a similar model adjusted for the same covariates, 1 h-PG (C-statistic 0.719 [95% CI 0.702, 0.736]) was also not significantly different ($p = 0.19$) from 2 h-PG (C-statistic 0.710 [95% CI 0.693, 0.728]; ESM Table 4). These results indicate that when used alone, 1 h-PG and 2 h-PG are comparable predictors. To further illustrate this result, Fig. 1 shows the predictive ROC curves (i.e. plot of sensitivity and 1–specificity) of 1 h-PG and 2 h-PG for predicting type 2 diabetes at 5 and 25 years for Group 2. The ROC curves for 1 h-PG and 2 h-PG are very similar at 5 years (Fig. 1a) and 25 years (Fig. 1b). In all, 15% of the population had a 2 h-PG of ≥ 7.8 mmol/l (cut-off point) for IGT. Using the same percentage as a target identified a 1 h-PG cut-off value of ≥ 9.3 mmol/l, with similar sensitivity and specificity at 5 years (34% and 88%, respectively) to the 2 h-PG cut-off (35% and 87%, respectively). Likewise, the sensitivity and specificity of 1 h-PG at 25 years (22% and 97%, respectively) is similar to those of 2 h-PG (23% and 97%, respectively). The point representing the 1 h-PG cut-off of ≥ 8.6 mmol/l, which was reported by others to maximise the sum of sensitivity and specificity [5], is shown in Fig. 1 for

Table 2 Pearson's correlation coefficients for glucose concentrations during OGTT with insulin action and secretion

Variable	OGTT time point				
	0 h	0.5 h	1 h	2 h	3 h
AIR ^a	−0.279	−0.243	−0.384	−0.281	−0.162
<i>M</i>	−0.323	−0.261	−0.340	−0.408	−0.378

Log₁₀ values were used for AIR (pmol/l) and *M* ($\mu\text{mol kg}_{\text{EMBS}}^{-1} \text{ min}^{-1}$)

^a Adjusted for *M*

$p < 0.001$ for all

Fig. 1 ROC curves based on the predicted cumulative incidence of type 2 diabetes by the Kaplan–Meier method for 1 h-PG (solid lines) and 2 h-PG (dashed lines) at (a) 5 years (AUC: 0.672 for 1 h-PG, 0.658 for 2 h-PG) and (b) 25 years (AUC: 0.728 for 1 h-PG, 0.706 for 2 h-PG). Blue diamond

(9.3 mmol/l) indicates the 1 h-PG cut-off closest to the 2 h-PG cut-off of 7.8 mmol/l (open grey triangle). Black triangle indicates the previously reported 1 h-PG cut-off (8.6 mmol/l) [5]

comparison. In our ROC curves, the points which maximised the sum of sensitivity and specificity at 5 years corresponded to ≥ 8.2 mmol/l for 1 h-PG and ≥ 6.9 mmol/l for 2 h-PG: these values had sensitivities of 52% and 51%, respectively, and specificities of 77% and 74%, respectively (not shown in Fig. 1). At 25 years, the points which maximised the sum of sensitivity and specificity corresponded to ≥ 7.2 mmol/l for 1 h-PG and ≥ 5.9 mmol/l for 2 h-PG: these values had sensitivities of 56% and 65%, respectively, and specificities of 79% and 67%, respectively.

To assess the benefit of combining 1 h-PG and 2 h-PG over either time point alone, risk prediction models including both 1 h-PG and 2 h-PG were also developed (ESM Table 3). For Group 1, after adjusting for covariates, 1 h-PG and 2 h-PG combined (C-statistic 0.755 [95% CI 0.720, 0.791]) did not significantly differ from comparable models involving 1 h-PG alone or 2 h-PG alone ($p = 0.23$ and $p = 0.20$, respectively). For Group 2 (ESM Table 4), after adjusting for the same covariates, models combining 1 h-PG and 2 h-PG (C-statistic 0.726 [95% CI 0.709, 0.743]) were significantly better compared with either 1 h-PG alone or 2 h-PG alone ($p = 0.01$ and $p < 0.001$, respectively), indicating the benefit of measuring both time points. However, the increase in C-statistic when both time points were combined was small compared with either 1 h-PG or 2 h-PG by themselves. A sensitivity analysis excluding the 108 participants from Group 2 who were already represented in Group 1 did not change the results (ESM Table 5).

To assess the contribution of fasting plasma glucose (FPG) to risk prediction models (ESM Table 3) involving 1 h-PG and 2 h-PG, additional models were evaluated for Group 1; these models also adjusted for the FPG and covariates described above (age, sex, BMI and SWNA heritage). Use of either 1 h-PG or 2 h-PG as the only glucose time point led to significantly greater C-statistics ($p < 0.001$ and 0.001 , respectively) compared with FPG (C-statistic 0.700 [95% CI 0.659, 0.741]).

Combining FPG and 1 h-PG (C-statistic 0.744 [95% CI 0.707, 0.780]) improved disease prediction compared with FPG alone ($p < .001$), but was not better than 1 h-PG alone ($p = 0.81$). Moreover, combining FPG with 1 h-PG was not significantly different from a model including FPG and 2 h-PG (C-statistic 0.750 [95% CI 0.713, 0.786]; $p = 0.62$), indicating that 1 h-PG has a similar ability to predict type 2 diabetes compared with 2 h-PG after accounting for FPG.

Discussion

We investigated the association of 1 h-PG and 2 h-PG with measures of insulin action (the HIEC) and insulin secretion (the IVGTT) among volunteers without type 2 diabetes. Our results indicated that although 2 h-PG was more closely associated with M compared with 1 h-PG, 1 h-PG was more closely associated with AIR. We then evaluated the ability of 1 h-PG and 2 h-PG to predict type 2 diabetes in two separate cohorts, and demonstrated that 1 h-PG and 2 h-PG have similar capabilities. When 1 h-PG and 2 h-PG were combined, the additional ability to predict type 2 diabetes was small, although it was statistically significant in the larger outpatient cohort; thus, combining both measures may not add meaningful clinical utility.

Consistent with previous reports [5, 6, 38], we showed that 1 h-PG by itself was a good predictor of type 2 diabetes. However, we found that 2 h-PG performed similarly to 1 h-PG, whereas other studies found that 1 h-PG was superior [5, 6, 38]. One explanation for the divergent results may be the different populations studied. The SWNA cohort included young adults with relatively high adiposity at baseline, while other studies included middle-aged adults with relatively lower adiposity at baseline who also differed with respect to race and ethnicity from our cohort [5, 6, 38], thus emphasising the importance of conducting studies in different populations. The

contradictory results may also be explained by different follow-up durations, which have been shown to influence the relative importance of glucose concentrations measured during the OGTT for predicting type 2 diabetes [7]. Group 1 participants also abstained from strenuous exercise and had eaten standardised diets for at least 3 days before the OGTT, representing a procedural difference from the other studies.

Using OGTT-based surrogate indices of insulin action and secretion, Abdul-Ghani et al found that 1 h-PG was more closely associated with both insulin action and secretion compared with 2 h-PG [5]. We found that 1 h-PG was more closely associated with AIR measured by IVGTT, a more accurate determination of insulin secretion. However, we found that 2 h-PG was more strongly associated with insulin action, which may explain why 1 h-PG and 2 h-PG had similar predictive abilities for type 2 diabetes in our population. Another explanation for the similar predictive abilities despite 1 h-PG being more strongly associated with insulin secretion is that 2 h-PG has demonstrated superior reproducibility compared with 1 h-PG when an OGTT is repeated [19]. Reproducibility, which influences sensitivity and specificity, is one criterion for evaluating a test. However, it is worth noting that despite its greater reproducibility, 2 h-PG was not a better predictor of type 2 diabetes in this study. Beyond issues of reproducibility or association with underlying pathophysiology, 1 h-PG and 2 h-PG are closely correlated measures ($r = -0.66$), which may also explain why they are comparable predictors. When choosing between the two, 1 h-PG may be preferable since it is logistically easier (i.e. shortened OGTT) and therefore more economical. However, it should be noted that models including both 1 h-PG and 2 h-PG were comparable with those involving either time point alone, indicating that using an OGTT with both time points does not confer a substantial advantage. Moreover, inclusion of FPG in models comparing 1 h-PG and 2 h-PG did not change the results: 1 h-PG remained comparable with 2 h-PG. Prediction models combining FPG with either 1 h-PG or 2 h-PG did not improve prediction of type 2 diabetes compared with either of the postload glucose time points alone. However, FPG is easy to obtain if an OGTT is being performed.

In this study, we identified a 1 h-PG cut-off (9.3 mmol/l) that was comparable with the 2 h-PG cut-off of 7.8 mmol/l for identifying individuals at elevated risk of type 2 diabetes. However, for 1 h-PG to be useful as a stand-alone time point, a cut-off for 1 h-PG that classifies type 2 diabetes is also needed. The 1979 National Diabetes Data Group criteria recommended using the same cut-off (i.e. 11.1 mmol/l) for both 2 h-PG and 1 h-PG [2]. This study showed that the equivalent cut-off between NGT and IGT for 1 h-PG was higher than that for 2 h-PG, suggesting that the optimal 1 h-PG cut-off for classifying type 2 diabetes should not be 11.1 mmol/l, but somewhere above this concentration.

Group 2 was analysed to provide additional confirmatory evidence that 1 h-PG and 2 h-PG are comparable predictors of

type 2 diabetes; the results were consistent with those of Group 1. However, baseline FPG was not generally available for Group 2 and some individuals may therefore have had type 2 diabetes based on FPG. However, those with type 2 diabetes based on FPG and known to be fasting were excluded from Group 1; findings for this group were consistent with those of Group 2. Also, we could not compare the predictive ability of 1 h-PG with HbA_{1c} since baseline visits for both Groups 1 and 2 occurred at times when HbA_{1c} measurement was not generally performed for diagnosing type 2 diabetes. Moreover, although it is possible that OGTT-based surrogates of insulin action and secretion can improve prediction, these typically require additional measurements (e.g. insulin) that are not routinely done in clinical practice.

In conclusion, 1 h-PG and 2 h-PG have similar abilities to predict future type 2 diabetes, and combining both measures has only a marginal benefit. Given that 1 h-PG can shorten the OGTT and present economic advantages over 2 h-PG, 1 h-PG should be considered an alternative postload glucose time point to identify those at elevated risk for type 2 diabetes.

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Data availability The datasets analysed during the current study are not publicly available for reasons of privacy but are available from Douglas C. Chang (changdc@mail.nih.gov) on reasonable request.

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