One-hour glucose value as a long-term predictor of cardiovascular morbidity and mortality: the Malmö Preventive Project

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Abstract

Objective: To examine the predictive capability of a 1-h vs 2-h postload glucose value for cardiovascular morbidity and mortality.

Design: Prospective, population-based cohort study (Malmö Preventive Project) with subject inclusion 1974–1992.

Methods: 4934 men without known diabetes and cardiovascular disease, who had blood glucose (BG) measured at 0, 20, 40, 60, 90 and 120 min during an OGTT (30 g glucose per m² body surface area), were followed for 27 years. Data on cardiovascular events and death were obtained through national and local registries. Predictive capabilities of fasting BG (FBG) and glucose values obtained during OGTT alone and added to a clinical prediction model comprising traditional cardiovascular risk factors were assessed using Harrell's concordance index (C-index) and integrated discrimination improvement (IDI).

Results: Median age was 48 (25th–75th percentile: 48–49) years and mean FBG 4.6 ± 0.6 mmol/L. FBG and 2-h postload BG did not independently predict cardiovascular events or death. Conversely, 1-h postload BG predicted cardiovascular morbidity and mortality and remained an independent predictor of cardiovascular death (HR: 1.09, 95% CI: 1.01–1.17, $P=0.02$) and all-cause mortality (HR: 1.10, 95% CI: 1.05–1.16, $P<0.0001$) after adjusting for various traditional risk factors. Clinical risk factors with added 1-h postload BG performed better than clinical risk factors alone, in predicting cardiovascular death (likelihood-ratio test, $P=0.02$) and all-cause mortality (likelihood-ratio test, $P=0.0001$; significant IDI, $P=0.0003$).

Conclusion: Among men without known diabetes, addition of 1-h BG, but not FBG or 2-h BG, to clinical risk factors provided incremental prognostic yield for prediction of cardiovascular death and all-cause mortality.

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Introduction

The strong influence of type 2 diabetes on the risk of cardiovascular morbidity and mortality is undisputed (1, 2), and effective measures to predict and prevent both type 2 diabetes and related cardiovascular complications are desirable.

Fasting blood glucose (FBG) alone is not sufficient in predicting hyperglycemia-related mortality, while the standard 2-h postload glucose value enables the detection of subjects with impaired glucose tolerance (IGT), who have a significantly increased risk of death (3).

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Furthermore, in overweight subjects with IGT, intensive lifestyle intervention and pharmacological treatment can prevent progression into overt type 2 diabetes and possibly ameliorate the risk of related cardiovascular complications (4, 5, 6). However, the 2-h OGTT has low sensitivity, has non-optimal specificity for incident diabetes and is time-consuming, and thus it is considered to carry limited cost-effectiveness and practicality (7). The past decade has seen several studies suggesting the superiority of a 1-h postload glucose value vs a 2-h postload glucose value for the prediction of type 2 diabetes (7, 8, 9, 10, 11, 12, 13, 14). Previous data from the Malmö Preventive Project have also shown that individuals at high risk for future type 2 diabetes can be identified using multivariable prediction models that include both FBG and blood glucose (BG) obtained during OGTT, with a significantly better predictive capability achieved for shorter OGTT regimens compared with both FBG and the classical 2-h OGTT (15). This might extend to cardiovascular morbidity and hyperglycemia-related mortality. Therefore, the primary purposes of the present study were (1) to evaluate the prognostic value of FBG and BG values obtained at different time points during OGTT, in predicting cardiovascular morbidity and mortality, both isolated and in addition to a multivariable prediction model; (2) to assess whether BG measured at 60 min during OGTT (BG₆₀) provided better prognostic yield than FBG and BG measured at 120 min (BG₁₂₀) and (3) to assess whether the prognostic value of BG₆₀ was influenced by glucose tolerance.

Subjects and methods

Study population

The Malmö Preventive Project (1974–1992, $n=33\ 346$) was a population-based cohort study conducted among inhabitants in Malmö, Sweden, belonging to pre-specified birth cohorts between 1921 and 1949 (16). Progressively older subjects were recruited later during the inclusion process. In all, 22 444 males and 10 902 females attended the screening program, with an overall attendance rate of 71% (75% for men). All subjects answered a self-administered questionnaire on lifestyle, family history of diabetes (first degree relatives) and cardiovascular disease, medical history and current medications. Current smoking was defined as smoking at least one cigarette daily, and sedentary lifestyle was defined as leisure time mostly spent on sedentary activities. Prevalent diabetes was defined as self-reported diabetes or according to the

1985 World Health Organization (WHO) criteria (17, 18). Prevalent cardiovascular disease was defined as self-reported cardiovascular disease (history of myocardial infarction (MI), stroke or transient ischemic attack) or according to national and local registries using the same diagnostic codes as for outcome (19). Height and weight in light indoor clothing were measured, from which body mass index (BMI) was calculated. Blood pressure was measured twice in the right arm after 10 min of supine rest, with the mean value recorded for analysis. Blood samples were obtained after ≥ 10 -h overnight fasting with measurement of BG, serum lipids and serum creatinine. BG levels were measured in capillary whole blood from fingertip samples and analyzed using the glucose-oxidase method (1974–1977) or the hexokinase method (1977–1992) (20). Serum samples were analyzed using the laboratory's standard methods. The Malmö Preventive Project was conducted in accordance with the Declaration of Helsinki.

Outcome

Follow-up time for each subject was defined as time elapsed from baseline screening to date of myocardial infarction, stroke, death, emigration or the last follow-up date up to 27 years. Cardiovascular events were recorded by national and local registries and comprised *International Classification of Diseases* (ICD-9) codes 410–414, 434, 430–438. Diagnosis of type 2 diabetes was recorded by 14 national and local registries and comprised *International Classification of Diseases* (ICD-10) codes E11.0–E11.9. The method to ascertain diagnosis of type 2 diabetes and cardiovascular events in the Swedish Inpatient Register has been previously validated (21). Positive predictive values were moderate for stroke and high for all other endpoints. Mortality follow-up was based on the national registry on causes of mortality at the Central Bureau of Statistics, Sweden.

Final study population

In participants without known diabetes, a 120-min OGTT was performed by ingestion of 30 g glucose per m² body surface area (DuBois equation) in a 10% aqueous solution within 5 min. BG levels were determined at 0, 20, 40, 60, 90 and 120 min. Subjects without an OGTT with extra BG measurements ($n=27\ 728$) were excluded from the present study, as were the 132 females of whom most did not have BG measured at the relevant intermediate time points. Remaining subjects with missing baseline variables ($n=70$)

Figure 1

Flowchart showing the study population selection.

or incomplete follow-up due to emigration ($n=70$) were likewise excluded. Of the 5346 male subjects left, 111 had prevalent diabetes and 301 had previous cardiovascular disease or received cardiovascular medication (antihypertensives, antithrombotics, antiarrhythmics), leaving a final study population comprising 4934 males (Fig. 1). Of note, 315 subjects with IGT (defined locally as $\text{BG}_{120} \geq 7.0 \text{ mmol/L}$) who underwent lifestyle intervention (dietary advice and increased physical activity, most often including frequent visits at an outpatient clinic) for up to 12 years upon confirmation of their IGT status were not excluded (22).

Statistical analysis

Continuous variables were summarized by means and standard deviations (approximately normally distributed variables) or medians and 25th and 75th percentiles (non-normally distributed variables). Categorical variables were presented by frequencies and corresponding percentages. Group-wise comparisons were performed using one-way analysis of variance (ANOVA), the Kruskal–Wallis test or Pearson's χ^2 -test, as appropriate. In order to define potential explanatory variables for the endpoints, i.e., incident myocardial infarction (nonfatal and fatal), stroke (nonfatal and fatal), death from cardiovascular causes and all-cause mortality, univariable Cox proportional-hazards regressions were applied on the following demographic and clinical variables: age, smoking status, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol,

triglycerides, creatinine, family history of diabetes and sedentary lifestyle. Since the distributions of serum triglycerides and creatinine were moderately positively skewed, they were both natural log-transformed for the regression analyses. Statistically significant and clinically relevant variables were included in the final multivariable Cox models, and stepwise backward elimination using the likelihood-ratio test was applied for adjustment of these models. The final regression model (clinical prediction model) included variables that were statistically significant in the multivariable models for at least one of the four endpoints. For BG, standardized values were calculated as the absolute value of FBG, BG_{60} or BG_{120} for each subject divided by each of their standard deviations. Furthermore, we used interaction analyses to test whether glucose (in)tolerance influenced the prognostic value of BG_{60} . This was done by including the interaction term for the continuous variable BG_{60} and the categorical variable, absence/presence of IGT, in the relevant regression models. The predictive abilities both alone and in addition to the clinical prediction model were tested with Harrell's concordance index (C-index) (23). The ability of each BG measurement during OGTT to enhance prognostication was also evaluated using integrated discrimination improvement (IDI) (24). Follow-up time was 27 years for all subjects without events, and supplementary analyses were done at shorter follow-up times (5, 10 and 20 years) to ensure that the results were independent of follow-up time. Analyses were focused on BG measured at 0, 60 and 120 min during OGTT because of the overall

better predictive capacity of BG₆₀ compared with BG measured at 20 and 40 min. BG measured at 90 min was comparable with BG₆₀, but since this measurement required 30 min extra, it seemed reasonable to exclude it (15). The significance level was 0.05 (two-sided), and given the exploratory nature of this study, no adjustments for multiple comparisons were made. All analyses were carried out using IBM SPSS Statistics 23 (IBM) and Stata/IC 14 (StataCorp LP).

Results

Characteristics of the study population

At baseline, median age was 48 (25th–75th percentile: 48–49) years, mean systolic blood pressure 130 ± 15 mmHg and mean BMI 24.8 ± 3.2 kg/m². Total cholesterol was 5.8 ± 1.0 mmol/L. Subjects with IGT at baseline ($n=301$) generally had a worse risk profile than their counterparts with NGT (Table 1). Similarly, a more adverse risk profile was present across BG₆₀ tertiles (Table 1). During follow-up, 1381 composite cardiovascular events (myocardial infarction, stroke or cardiovascular death, whichever came first) were detected, corresponding to 12.3 cases per 1000 person-years. A total of 1517 individuals had died from any cause. IGT and the uppermost BG₆₀ tertile appeared to be associated with poorer outcomes compared with NGT and the lower BG₆₀ tertiles, respectively (Table 2).

The clinical prediction model

The following variables were statistically significant on univariable analysis for prediction of incident nonfatal plus fatal myocardial infarction and nonfatal plus fatal stroke: age, active smoking, BMI, systolic blood pressure, total cholesterol and triglycerides. Sedentary lifestyle and creatinine were significant on univariable analysis for prediction of cardiovascular death and all-cause mortality. The final Cox regression model (clinical prediction model) included age, active smoking, BMI, systolic blood pressure, total cholesterol, triglycerides and creatinine. This model performed better than anyone isolated BG measurement for the prediction of all endpoints, with C-index for the former being highest for cardiovascular death (C-index=0.682, 95% confidence interval (CI): 0.66–0.70), followed by myocardial infarction (C-index=0.666, 95% CI: 0.65–0.69), all-cause mortality (C-index=0.638, 95% CI: 0.62–0.65) and stroke (C-index=0.612, 95% CI: 0.59–0.63).

Table 1 Baseline characteristics according to glucose tolerance status and BG₆₀ tertile group at baseline, respectively. Categorical variables are presented as n (%), whereas continuous, approximately normally distributed variables are presented as mean $\pm$ s.d., and continuous, non-normally distributed variables are presented as median (IQR).

Variable	All subjects ($n=4934$)	NGT ($n=4633$)	IGT ($n=301$)	P values	BG ₆₀ tertile 1 ($n=1641$)	BG ₆₀ tertile 2 ($n=1648$)	BG ₆₀ tertile 3 ($n=1645$)	P values
Age (years)	48 (48–49)	48 (48–49)	48 (48–49)	0.4 [‡]	48 (48–49)	48 (48–49)	48 (48–49)	<0.0001
Active smoking	2612 (53%)	2487 (54%)	125 (42%)	<0.0001 [‡]	803 (49%)	863 (52%)	946 (58%)	<0.0001 [*]
BMI (kg/m ²)	24.8 ± 3.2	24.7 ± 3.1	26.1 ± 3.5	<0.0001 [†]	24.2 ± 2.9	24.8 ± 3.2	25.2 ± 3.4	<0.0001 [§]
Systolic BP (mmHg)	130 ± 15	129 ± 15	140 ± 19	<0.0001 [†]	126 ± 13	129 ± 15	135 ± 17	<0.0001 [§]
TC (mmol/L)	5.8 ± 1.0	5.8 ± 1.0	6.0 ± 1.1	0.001 [†]	5.7 ± 1.0	5.8 ± 1.0	5.8 ± 1.0	<0.0001 [§]
Triglycerides (mmol/L)	$1.4 (1.0–1.9)$	$1.4 (1.0–1.8)$	$1.7 (1.2–2.3)$	<0.0001 [†]	$1.3 (1.0–1.6)$	$1.4 (1.1–1.8)$	$1.5 (1.1–2.1)$	<0.0001
Creatinine (pmol/L)	$94 (86–102)$	$94 (86–102)$	$91 (85–101)$	0.2 [‡]	$95 (87–103)$	$94 (86–102)$	$93 (85–101)$	0.001
FBG (mmol/L)	4.6 ± 0.6	4.6 ± 0.5	5.0 ± 0.6	<0.0001 [†]	4.4 ± 0.5	4.6 ± 0.5	4.9 ± 0.6	<0.0001 [§]
60 min PLBG (mmol/L)	8.1 ± 2.1	7.9 ± 2.0	10.6 ± 1.9	<0.0001 [†]	6.0 ± 0.8	7.9 ± 0.5	10.4 ± 1.5	<0.0001 [§]
120 min PLBG (mmol/L)	5.4 ± 1.5	5.1 ± 1.2	8.7 ± 0.8	<0.0001 [†]	4.8 ± 1.1	5.2 ± 1.2	6.1 ± 1.7	<0.0001 [§]
Sedentary lifestyle	2797 (57%)	2605 (56%)	192 (64%)	0.01 [*]	881 (54%)	924 (56%)	992 (60%)	0.001 [*]

^{*}Pearson's χ^2 -test; [†]independent samples t -test; [‡]Mann–Whitney U test; [§]one-way ANOVA; ^{||}Kruskal–Wallis test.

BP, blood pressure; FBG, fasting blood glucose; PLBG, post load blood glucose; BG₆₀, blood glucose measured at 60 min during OGTT; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Table 2 Impact of glucose tolerance status and BG₆₀ tertile group on number of events and event rates per 1000 person-years.

	Total (n=4934)	Normal glucose tolerance (NGT) (n=4633)	Impaired glucose tolerance (IGT) (n=301)	P values for difference between NGT and IGT	BG ₆₀ tertile 1 (n=1641)	BG ₆₀ tertile 2 (n=1648)	BG ₆₀ tertile 3 (n=1645)	P values for difference between BG ₆₀ tertiles
All-cause mortality	1517 (12.7)	1407 (12.6)	110 (15.1)	0.02*	418 (10.5)	494 (12.4)	605 (15.2)	<0.0001*
Cardiovascular death	638 (5.4)	584 (5.2)	54 (7.4)	0.008*	156 (3.9)	221 (5.6)	261 (6.6)	<0.0001*
Myocardial infarction (nonfatal and fatal)	763 (6.7)	712 (6.7)	51 (7.3)	0.5*	213 (5.6)	253 (6.7)	297 (7.8)	<0.0001*
Stroke (nonfatal and fatal)	455 (3.9)	432 (3.9)	23 (3.2)	0.3*	130 (3.3)	151 (3.9)	174 (4.5)	0.03*
Nonfatal myocardial infarction	592 (5.2)	552 (5.2)	40 (5.8)	0.5*	177 (4.7)	188 (4.9)	227 (6.0)	0.02*
Fatal myocardial infarction	171 (1.4)	160 (1.4)	11 (1.5)	0.9*	36 (0.9)	65 (1.6)	70 (1.8)	0.002*
Nonfatal stroke	419 (3.6)	398 (3.6)	21 (2.9)	0.3*	121 (3.1)	138 (3.5)	160 (4.1)	0.052*
Fatal stroke	36 (0.3)	34 (0.3)	2 (0.3)	0.9*	9 (0.2)	13 (0.3)	14 (0.4)	0.6*

*Pearson's χ^2 -test.BG₆₀, blood glucose measured at 60 min during OGTT; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Fasting blood glucose and postload glucose values

At 27 years, BG₆₀ alone was a significant predictor of fatal myocardial infarction (hazard ratio (HR): 1.22, 95% CI: 1.09–1.36, $P=0.0006$), nonfatal myocardial infarction (HR: 1.10, 95% CI: 1.02–1.18, $P=0.01$), nonfatal plus fatal myocardial infarction (HR: 1.13, 95% CI: 1.06–1.20, $P=0.0001$), nonfatal plus fatal stroke (HR: 1.14, 95% CI: 1.06–1.24, $P=0.0008$), nonfatal stroke (HR: 1.14, 95% CI: 1.05–1.24, $P=0.002$), death from cardiovascular causes (HR: 1.21, 95% CI: 1.14–1.28, $P<0.0001$) and all-cause mortality (HR: 1.18, 95% CI: 1.14–1.23, $P<0.0001$). BG₁₂₀ and FBG alone did not predict any of the endpoints (Table 3). At 20 years of follow-up, BG₁₂₀ alone predicted cardiovascular death (HR: 1.13, 95% CI: 1.02–1.25, $P=0.02$), whereas FBG still did not predict any of the endpoints ($P\geq 0.21$ for all), and BG₆₀ remained superior to both ($P<0.0001$).

Fatal myocardial infarction was detected in 171 subjects, and fatal stroke was detected in 36 subjects. Accordingly, fatal myocardial infarction contributed the most to cardiovascular death. C-index for BG₆₀ alone was consistently greater than that for FBG or BG₁₂₀ (Table 4); however, significant comparisons were only observed for all-cause mortality, cardiovascular death, nonfatal plus fatal myocardial infarction and nonfatal plus fatal stroke ($P\leq 0.02$; $P>0.05$ for the comparison with FBG (myocardial infarction) and for the comparison with BG₁₂₀ (stroke)). The presence of IGT at baseline significantly interacted with the association between BG₆₀ and all-cause mortality ($P=0.001$), cardiovascular death ($P=0.0004$) and nonfatal plus fatal stroke ($P=0.03$), with higher predictive values of BG₆₀ found among subjects with IGT at baseline (Fig. 2A, B, C and D). When BG₆₀ and BG₁₂₀ were both analyzed as continuous variables, BG₁₂₀ modified the association between BG₆₀ and myocardial infarction ($P=0.03$).

The intervention, carried out in a minority of the study subjects, did not alter the estimates and did not interact with the association between any BG measurement and any endpoint ($P>0.05$ for all). Furthermore, incident type 2 diabetes during follow-up did not interact with any association between BG₆₀ and the endpoints ($P\geq 0.50$ for all).

Fasting blood glucose and oral glucose tolerance test in combination with the clinical prediction model

After adjusting for the variables included in the clinical prediction model, neither FBG nor BG₁₂₀ predicted any of the endpoints. However, BG₆₀ remained independently

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Table 3 Hazard ratios for different standardized glucose values at 27-years of follow-up, unadjusted, age-adjusted and fully adjusted for age, active smoking, BMI, systolic blood pressure, total cholesterol, triglycerides and creatinine.

	All-cause mortality (n=1517)		Cardiovascular death (n=638)		Nonfatal and fatal MI (n=763)		Nonfatal and fatal stroke (n=455)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Unadjusted								
FBG	1.01 (0.96–1.06)	NS	1.01 (0.94–1.10)	NS	1.04 (0.97–1.12)	NS	1.01 (0.92–1.11)	NS
BG ₆₀	1.18 (1.14–1.23)	<0.0001	1.21 (1.14–1.28)	<0.0001	1.13 (1.06–1.20)	0.0001	1.14 (1.06–1.24)	0.0008
BG ₁₂₀	0.97 (0.92–1.02)	NS	1.04 (0.96–1.13)	NS	1.03 (0.96–1.10)	NS	0.96 (0.87–1.05)	NS
Age adjusted								
FBG	1.05 (1.00–1.11)	NS	1.08 (1.00–1.16)	NS	1.07 (1.00–1.15)	NS	1.05 (0.96–1.15)	NS
BG ₆₀	1.18 (1.14–1.23)	<0.0001	1.21 (1.14–1.28)	<0.0001	1.13 (1.06–1.20)	0.0002	1.14 (1.06–1.24)	0.0008
BG ₁₂₀	0.97 (0.92–1.02)	NS	1.04 (0.96–1.13)	NS	1.03 (0.96–1.10)	NS	0.96 (0.87–1.05)	NS
Fully adjusted								
FBG	1.00 (0.94–1.05)	NS	0.98 (0.90–1.06)	NS	0.97 (0.90–1.05)	NS	0.98 (0.89–1.08)	NS
BG ₆₀	1.10 (1.05–1.16)	<0.0001	1.09 (1.01–1.17)	0.02	1.0 (0.93–1.07)	NS	1.06 (0.97–1.16)	NS
BG ₁₂₀	0.97 (0.92–1.03)	NS	0.98 (0.91–1.07)	NS	0.97 (0.90–1.05)	NS	0.89 (0.80–0.98)	0.02
Fully adjusted and further adjusted for FBG								
BG ₆₀	1.11 (1.06–1.17)	<0.0001	1.10 (1.03–1.19)	0.009	1.01 (0.93–1.09)	NS	1.07 (0.98–1.18)	NS
BG ₁₂₀	0.97 (0.92–1.03)	NS	0.99 (0.91–1.08)	NS	0.97 (0.90–1.05)	NS	0.89 (0.80–0.98)	0.02

FBG, BG₆₀ and BG₁₂₀ are standardized using their standard deviations: 0.6, 2.1 and 1.5 mmol/L, respectively. BG₆₀, blood glucose measured at 60 min during OGTT; BG₁₂₀, blood glucose measured at 120 min during OGTT; FBG, fasting blood glucose; MI, myocardial infarction.

predictive of all-cause mortality (adjusted HR: 1.10, 95% CI: 1.05–1.16, $P<0.0001$) and cardiovascular death (adjusted HR: 1.09, 95% CI: 1.01–1.17, $P=0.02$) (Table 3). The predictive value of the fully adjusted BG₆₀ model was also highest in subjects with IGT at baseline (Fig. 2A, B, C and D). Adjusting for FBG did not reduce the predictive value of BG₆₀ (Table 3).

Adding BG₆₀ to the clinical prediction model significantly improved the prediction of all-cause mortality (likelihood-ratio test; $P=0.0001$) and cardiovascular death (likelihood-ratio test; $P=0.02$), although with no significant C-index increment. Addition of FBG or BG₁₂₀ did not provide model improvement (likelihood-ratio test; $P\geq 0.21$ for all). BG₆₀ was further associated with significant IDI in predicting all-cause mortality ($P=0.0003$). Conversely, BG₁₂₀ was associated with a significant IDI in predicting stroke ($P=0.02$), but the HR for BG₁₂₀ was <1 in the fully adjusted prediction model.

The overall results did not change using shorter follow-up (Table 5).

Discussion

Our results show that among apparently healthy, middle-aged men without known diabetes, BG measured at 60 min during OGTT provides better prognostic yield than both FBG and BG measured at 120 min, in predicting long-term cardiovascular morbidity and mortality, both isolated and in addition to a clinical prediction model.

The conventional 2-h postload glucose value is known to be a significant, independent and better predictor of cardiovascular morbidity and mortality than fasting glucose (3, 25, 26, 27, 28). We found a significant prediction of cardiovascular death with BG₁₂₀, although only unadjusted, and no significant predictive value of FBG. However, the association between BG₁₂₀ and cardiovascular death was only evident on supplementary analyses with a shorter follow-up time. The predictive capacity might have been diluted over time, given the old age, co-morbidity status and age-related events at the time of study completion. An additional explanation may be our relatively healthy (from a glucometabolic perspective) cohort, in which both fasting and 2-h glucose values generally were low and rarely reached the criteria for prediabetes. In contrast, other studies have largely evaluated persons with higher glucose values closer to or even fulfilling contemporary prediabetes criteria. The interventional program of lifestyle changes in most subjects with baseline IGT decreased mortality at 12 years

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Table 4 Harrell's C-indices for different glucose values at 27-years of follow-up alone and in addition to the clinical prediction model, which included age, active smoking, BMI, systolic blood pressure, total cholesterol, triglycerides and creatinine.

	All-cause mortality	Cardiovascular death	Nonfatal and fatal MI	Nonfatal and fatal stroke
Alone				
FBG	0.503	0.503	0.515	0.497
BG ₆₀	0.557	0.567	0.543	0.546
BG ₁₂₀	0.515	0.503	0.506	0.516
P^a	<0.001	<0.001 ^a	0.06	0.02
P^b	0.002	<0.001	0.02	0.3
Together with the clinical prediction model				
FBG	0.638	0.682	0.667	0.612
BG ₆₀	0.641	0.685	0.666	0.613
BG ₁₂₀	0.638	0.682	0.666	0.616
FBG + BG ₆₀	0.642	0.685	0.667	0.613
FBG + BG ₁₂₀	0.638	0.682	0.666	0.616
FBG + BG ₆₀ + BG ₁₂₀	0.643	0.685	0.666	0.618

P values are for comparisons of Harrell's C-indices for BG₆₀ vs Harrell's C-indices for ^aFBG and ^bBG₁₂₀, respectively.

BG₆₀, blood glucose measured at 60 min during OGTT; BG₁₂₀, blood glucose measured at 120 min during OGTT; FBG, fasting blood glucose; MI, myocardial infarction.

(22), but there was no effect on long-term outcome (29). Furthermore, the local threshold for baseline IGT was rather low (7.0 rather than 7.8 mmol/L). This is likely to have resulted in a rather large number of subjects at moderate-to-high risk being captured. Still, excluding all subjects with IGT would have lowered the variability in observed BG levels substantially and excluded a large number of individuals at high risk for clinical events.

Despite the above, BG₆₀ significantly predicted myocardial infarction, stroke, cardiovascular death and all-cause mortality, and after adjustment for other cardiovascular risk factors, BG₆₀ still predicted cardiovascular death and all-cause mortality. Lending support to our results, Orenca and coworkers (30) demonstrated that 1-h postload glucose was an independent risk factor for all-cause mortality at

Figure 2

(A) Prediction of all-cause mortality by blood glucose obtained at 60-min OGTT in subjects with and without impaired glucose tolerance at baseline both unadjusted and fully adjusted for age, active smoking, BMI, systolic blood pressure, total cholesterol, triglycerides and creatinine. Hazard ratios are calculated for absolute, unstandardized glucose values. NGT, normal glucose tolerance; IGT, impaired glucose tolerance. (B) Prediction of cardiovascular mortality by blood glucose obtained at 60 min during OGTT in subjects with and without impaired glucose tolerance at baseline both unadjusted and fully adjusted for age, active smoking, BMI, systolic blood pressure, total cholesterol, triglycerides and creatinine. Hazard ratios are calculated for absolute, unstandardized glucose values. NGT, normal glucose tolerance; IGT, impaired glucose tolerance. (C). Prediction of myocardial infarction (nonfatal + fatal) by blood glucose obtained at 60 min during OGTT test in subjects with and without impaired glucose tolerance at baseline both unadjusted and fully adjusted for age, active smoking, BMI, systolic blood pressure, total cholesterol, triglycerides and creatinine. Hazard ratios are calculated for absolute, unstandardized glucose values. NGT, normal glucose tolerance; IGT, impaired glucose tolerance. (D) Prediction of stroke (nonfatal + fatal) by blood glucose obtained at 60 min during OGTT in subjects with and without impaired glucose tolerance at baseline both unadjusted and fully adjusted for age, active smoking, BMI, systolic blood pressure, total cholesterol, triglycerides and creatinine. Hazard ratios are calculated for absolute, unstandardized glucose values. NGT, normal glucose tolerance; IGT, impaired glucose tolerance.

Table 5 Hazard ratios and Harrell's C-indices for different standardized glucose values at 5, 10 and 20 years of follow-up, unadjusted and fully adjusted for age, active smoking, BMI, systolic blood pressure, total cholesterol, triglycerides, creatinine and fasting blood glucose.

	All-cause mortality (n=810 at 20 years)				Cardiovascular death (n=356 at 20 years)				Nonfatal and fatal MI (n=516 at 20 years)				Nonfatal and fatal stroke (n=198 at 20 years)			
	HR (95% CI)	C-index	Harrell's P-Value	HR (95% CI)	C-index	Harrell's P-Value	HR (95% CI)	C-index	Harrell's P-Value	HR (95% CI)	C-index	Harrell's P-Value	HR (95% CI)	C-index	Harrell's P-Value	
5 years of follow-up																
Unadjusted																
FBG	1.04 (0.85–1.26)	0.507	NS	1.08 (0.77–1.51)	0.514	NS	1.03 (0.83–1.29)	0.502	NS	0.93 (0.48–1.80)	0.505	NS				
BG ₆₀	1.26 (1.10–1.44)	0.580	0.001	1.26 (1.00–1.59)	0.574	NS	1.29 (1.12–1.48)	0.609	<0.001	1.26 (0.80–1.98)	0.585	NS				
BG ₁₂₀	0.95 (0.77–1.16)	0.524	NS	1.10 (0.80–1.53)	0.517	NS	1.19 (0.97–1.47)	0.544	NS	1.17 (0.63–2.18)	0.567	NS				
Fully adjusted																
BG ₆₀	1.17 (0.99–1.39)	0.693	NS	1.11 (0.79–1.56)	0.777	NS	1.18 (0.98–1.42)	0.756	NS	1.21 (0.70–2.07)	0.713	NS				
BG ₁₂₀	0.92 (0.74–1.15)	0.689	NS	0.99 (0.69–1.41)	0.772	NS	1.15 (0.92–1.45)	0.753	NS	1.15 (0.57–2.31)	0.709	NS				
10 years of follow-up																
Unadjusted																
FBG	1.11 (0.98–1.25)	0.521	NS	1.22 (1.01–1.47)	0.547	0.04	1.08 (0.94–1.23)	0.522	NS	0.73 (0.51–1.05)	0.589	NS				
BG ₆₀	1.24 (1.13–1.35)	0.570	<0.001	1.29 (1.14–1.45)	0.591	<0.001	1.17 (1.05–1.31)	0.557	0.005	1.30 (1.05–1.61)	0.593	0.02				
BG ₁₂₀	1.05 (0.93–1.18)	0.499	NS	1.16 (0.96–1.39)	0.520	NS	1.05 (0.92–1.20)	0.515	NS	0.99 (0.69–1.41)	0.502	NS				
Fully adjusted																
BG ₆₀	1.13 (1.01–1.26)	0.667	0.03	1.13 (0.95–1.36)	0.715	NS	1.01 (0.87–1.16)	0.725	NS	1.28 (1.02–1.61)	0.795	0.03				
BG ₁₂₀	1.02 (0.89–1.16)	0.664	NS	1.03 (0.85–1.26)	0.711	NS	0.99 (0.85–1.14)	0.726	NS	1.10 (0.76–1.59)	0.780	NS				
20 years of follow-up																
Unadjusted																
FBG	1.04 (0.98–1.12)	0.510	NS	1.07 (0.96–1.19)	0.515	NS	1.05 (0.96–1.14)	0.514	NS	1.02 (0.88–1.17)	0.497	NS				
BG ₆₀	1.21 (1.14–1.27)	0.566	<0.001	1.24 (1.15–1.33)	0.580	<0.001	1.12 (1.03–1.21)	0.539	0.006	1.15 (1.02–1.29)	0.547	0.03				
BG ₁₂₀	0.98 (0.91–1.05)	0.515	NS	1.13 (1.02–1.25)	0.520	0.02	1.03 (0.95–1.13)	0.505	NS	0.92 (0.79–1.06)	0.530	NS				
Fully adjusted																
BG ₆₀	1.12 (1.05–1.19)	0.656	<0.001	1.12 (1.01–1.24)	0.699	0.03	0.97 (0.88–1.07)	0.690	NS	1.04 (0.90–1.21)	0.662	NS				
BG ₁₂₀	0.96 (0.89–1.03)	0.652	NS	1.03 (0.93–1.16)	0.696	NS	0.97 (0.88–1.06)	0.690	NS	0.85 (0.72–0.99)	0.662	0.04				

FBG, BG₆₀ and BG₁₂₀ are standardized using their standard deviations: 0.6, 2.1 and 1.5 mmol/L, respectively.BG₆₀, blood glucose measured at 60 min during OGTT; BG₁₂₀, blood glucose measured at 120 min during OGTT; FBG, fasting blood glucose; MI, myocardial infarction.

long-term (22 years) follow-up in middle-aged men without diabetes. Higher postload glucose levels were also independent risk factors for the major cardiovascular diseases. However, there was no direct comparison with fasting or 2-h glucose measurements. This was also the case for a 44-year prospective study, in which a strong and graded relationship was found between 1-h glucose quartiles and both total and cardiovascular mortality, independently of traditional cardiovascular risk factors, in men without diabetes (31). In a third study by Meisinger and coworkers (32), it was likewise established that a higher 1-h postload glucose value was an independent long-term (up to 30 years) predictor of all-cause mortality. However, the investigators used a very high partition value (200 mg/dL = 11.1 mmol/L) and did not provide a comparison with fasting or 2-h glucose values. Data from the Finnish Diabetes Prevention Study showed that among persons with IGT, both 1-h and 2-h plasma glucose values and their temporal patterns were significantly associated with cardiovascular events (myocardial infarction, stroke, unstable angina, coronary artery bypass graft or percutaneous coronary intervention), although only the 2-h glucose remained significant in pairwise comparisons (33). Concerning reclassification abilities, Bergman and coworkers (7) found that a 1-h glucose value >155 mg/dL (>8.6 mmol/L) predicted mortality among individuals in whom the 2-h level was <140 mg/dL (<7.8 mmol/L). Finally, an elaborate study by Hulman and coworkers identified four distinct glucose patterns during an OGTT with glucose measurements at 0, 30 and 120 min. Among these healthy participants without diabetes at baseline, the risks of incident diabetes and of all-cause mortality were significantly increased with an elevated glucose level at 30 min, risks that were independent of glucose levels at 0 and 120 min (34). The same group of authors was also involved in another study of glucose response curves during OGTT, in which they observed a variety of responses despite similar fasting and 2-h glucose values. These responses differed with respect to their associations with cardiovascular and metabolic risk factors. This in and of itself suggests the usefulness of an intermediate, i.e., between 0 and 120 min, measurement of postload glucose (35).

Influence of impaired glucose tolerance at baseline

The interactions with IGT and the association between BG₆₀ and all-cause mortality, cardiovascular death and stroke, may suggest that elevated BG₆₀ does not merely precede elevated BG₁₂₀, as a smaller effect of increased

BG₆₀ in subjects with increased BG₁₂₀ would then be expected. Possibly, having both abnormal BG₆₀ and BG₁₂₀ increases the possibility of correct categorization. Still, the interactions for the continuous BG variables suggest other explanations. One very interesting hypothesis could be that high BG₆₀ is particularly harmful, from a cardiovascular perspective, if allowed to stay elevated for at least 60 additional minutes. Accordingly, these interactions may reflect a dissociation between prediction of type 2 diabetes and cardiovascular events, as both BG₆₀ and BG₁₂₀ appear to be markers of prediabetes, while the mechanisms by which BG₆₀ and BG₁₂₀ predict cardiovascular events seemingly differ (33). Finally, it must be emphasized that the intervention program of lifestyle changes may have influenced the results, although given the interaction between BG₆₀ and BG₁₂₀, this does not seem to be the case at long-term follow-up.

Postload glucose values and clinical risk factors

Addition of BG₆₀ to traditional cardiovascular risk factors significantly improved the predictive capability, and there was also significant IDI in the prediction of all-cause mortality, when adding BG₆₀ to these risk factors. Conversely, Stern and coworkers (36) did not find a significant model improvement after addition of the standard 2-h postload glucose measurement to a clinical prediction model. The investigators thus suggested that prediction models should only include readily available clinical variables. Obviously, this is attractive because of the ease of administration, convenience, acceptability to screened subjects and lower cost. However, since the burden of type 2 diabetes and complications is rapidly rising, we believe that subjects at high risk of developing IGT and type 2 diabetes could be identified earlier using BG₆₀. It is very likely that in subjects with an abnormal BG₆₀, lifestyle intervention may prevent progression to IGT, type 2 diabetes, cardiovascular events and ultimately death.

Influence of development of type 2 diabetes during follow-up

Another question that appears is whether such elevated cardiovascular risk is restricted to individuals who develop diabetes during follow-up, but in the present study, incident type 2 diabetes did not significantly interact with the association between BG₆₀ and incident cardiovascular events or death. Only few studies have explored this because of the absence of follow-up data

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on diabetes diagnosis; however, in accordance with our findings, Qiao and coworkers (37) demonstrated that baseline IGT, although defined by the standard 2-h OGTT, was an independent predictor for 10-year cardiovascular morbidity and mortality as well as total mortality, not confounded by the subsequent development of diabetes.

Limitations

A comparison between HbA_{1c} and glucose values obtained during OGTT would have been desirable, but such measurements were not done. OGTT was performed only at baseline and therefore subjected to regression dilution bias (38). Furthermore, at the time of inclusion, a standard OGTT comprised a 30 g/m² glucose load which, however, seems to yield results similar to the standard 75 g load (39). Our exclusion of a significant proportion of the original study population, although based on financial reasons (lack of extra BG measurements), constitutes a major limitation and prevents us from extending our results beyond middle-aged white men. Additionally, the lifestyle intervention performed in subjects with IGT at baseline may potentially have influenced the predictive capability of the 2-h glucose measurement, even though the follow-up data and analyses did not indicate this in neither the present nor in a previous study (29). In fact, excluding these subjects at the highest likelihood of developing type 2 diabetes and as such, the outcomes examined in this study, might have underestimated the true risk of complications. Despite significant differences in several comparisons between the prediction models, the discriminative values and their numerical differences were of limited magnitude. This may suggest limited clinical relevance. However, follow-up time was very long, which attenuated the discriminative ability of all models as previously shown (15). Furthermore, it should be remembered that prediction models generally tend to overestimate the actual event risk when applied to the population from which they were derived (40). Lastly, different between-study results might further be due to variations in sex ratio, ethnicity, sample sizes, inclusion criteria, co-variables included, glucose load used for OGTT, follow-up duration and definition of outcome variables.

Clinical perspectives

Shorter examination time is associated with lower cost and greater convenience for both patients and health care professionals. Although the introduction of HbA_{1c} as a diagnostic tool for diabetes has led to performance

of fewer OGTTs, it is well known that these methods display limited concordance (41). Therefore, a role for OGTT likely exists in subjects with a high normal or an only slightly elevated HbA_{1c}, in order to reach a definitive diagnostic decision. With an increasing number of studies demonstrating a strong superior capacity compared with FBG and the 2-h glucose value in identifying subjects with a high risk of developing type 2 diabetes and related complications, it seems reasonable to consider the 1-h glucose value in order to benefit from early prevention in subjects with high risk of future type 2 diabetes and cardiovascular complications. Still, our findings need replication and external validation. In addition, interventional studies are necessary to prove the benefit of secondary prevention in high-risk individuals found through non-traditional methods.

In conclusion, in this prospective population-based cohort study, we found an OGTT-derived 60-min BG provided better prognostic value than FBG or 120-min postload BG, in predicting long-term cardiovascular morbidity and mortality, in apparently healthy, middle-aged, men without known diabetes.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

Mette Nielsen contributed substantially to the conception of the hypothesis, the design of the work, analysis of the work, interpretation of data for the work, drafting the work, critical revision for important intellectual content, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Manan Pareek contributed substantially to the conception of the hypothesis, the design of the work, analysis of the work, critical revision for important intellectual content, final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Margrét Leósdóttir, Karl-Fredrik Eriksson and Peter M Nilsson contributed substantially to the acquisition of data for the work, critical revision for important intellectual content, the final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Michael Olsen contributed substantially to the conception of the hypothesis, the design of the work, analysis of the work, interpretation of data for the work, drafting the work, critical revision for important intellectual content, final approval of the version to be published and

agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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