Enhanced Predictive Capability of a 1-Hour Oral Glucose Tolerance Test: A Prospective Population-Based Cohort Study

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OBJECTIVE
To examine whether the 1-h blood glucose measurement would be a more suitable screening tool for assessing the risk of diabetes and its complications than the 2-h measurement.

RESEARCH DESIGN AND METHODS
We conducted a prospective population-based cohort study of 4,867 men, randomly selected from prespecified birth cohorts between 1921 and 1949, who underwent an oral glucose tolerance test with blood glucose measurements at 0, 1, and 2 h. Subjects were followed for up to 39 years, with registry-based recording of events. Discriminative abilities of elevated 1-h (≥8.6 mmol/L) versus 2-h (≥7.8 mmol/L) glucose for predicting incident type 2 diabetes, vascular complications, and mortality were compared using Kaplan-Meier analysis, Cox proportional hazards regression, and net reclassification improvement.

RESULTS
Median age was 48 years (interquartile range [IQR] 48–49). During follow-up (median 33 years [IQR 24–37]), 636 (13%) developed type 2 diabetes. Elevated 1-h glucose was associated with incident diabetes (hazard ratio 3.40 [95% CI 2.90–3.98], \( P < 0.001 \)) and provided better risk assessment than impaired glucose tolerance (Harrell concordance index 0.637 vs. 0.511, \( P < 0.001 \)). Addition of a 1-h measurement in subjects stratified by fasting glucose provided greater net reclassification improvement than the addition of a 2-h measurement (0.214 vs. 0.016, respectively). Finally, the 1-h glucose was significantly associated with vascular complications and mortality.

CONCLUSIONS
The 1-h blood glucose level is a stronger predictor of future type 2 diabetes than the 2-h level and is associated with diabetes complications and mortality.

Type 2 diabetes is associated with significant morbidity and mortality and represents a major burden on health care systems worldwide (1,2). Several randomized clinical trials provide evidence that type 2 diabetes can be prevented or at least postponed with lifestyle modification and drug therapy, which makes identifying high-risk individuals particularly important (3–6). Traditionally, prediabetes has been defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) during a 2-h oral glucose tolerance test (OGTT), and interventional studies thus far have predominantly included subjects with IGT (7,8). However, not all subjects with prediabetes develop type 2
diabetes, and conversely, a significant number without prediabetes progress to type 2 diabetes (9). Accumulating longitudinal evidence, pioneered in particular by Abdul-Ghani and colleagues (10–18), suggests that the 1-h postload glucose level during OGTT with a cutoff ≥8.6 mmol/L (155 mg/dL) may be an early marker of IGT and subsequent type 2 diabetes that is potentially more useful than either fasting or 2-h glucose levels. Furthermore, from a pathophysiological perspective, the 1-h glucose level is intriguing owing to its seemingly strong correlation with markers of both insulin secretion and sensitivity (10,19,20). However, practical clinical implications of using a 1-h glucose measurement for prediction of type 2 diabetes and its associated complications are less clear. Therefore, the aim of this study was to examine whether the 1-h blood glucose measurement would be a more suitable screening tool for risk assessment than the 2-h blood glucose alone.

RESEARCH DESIGN AND METHODS

All subjects were participants of the Malmö Preventive Project (1974–1992), a population-based case-finding program with the objective of identifying high-risk adults suitable for preventive measures. Inhabitants of Malmö, Sweden, belonging to prespecified birth cohorts (1921–1949) were invited for an examination of cardiovascular risk factors, alcohol abuse, and breast cancer. Progressively older men were recruited later during the course of the study. The participation rate was 71% (21–23). During the initial phase of the study (9 September 1974 to 31 May 1978 [both inclusive]), 7,200 men were consecutively included, of whom 5,364 underwent baseline OGTT. After exclusion of subjects with a missing or invalid 1-h glucose measurement (7 of 5,364) or known diabetes (100 of 5,364), and those who emigrated (71 of 5,364), 5,182 individuals were left. Of these, a subset of individuals at high risk—including those with hypertension, hyperlipidemia, diabetes, and IGT, with the latter defined per local standards as a 2-h blood glucose level ≥7.0 mmol/L (126 mg/dL) confirmed on a separate day (315 of 5,182)—underwent intervention. The intervention for IGT comprised of dietary advice and increased physical activity, most often including frequent visits at an outpatient clinic for up to 12 years after inclusion. We also excluded these subjects; thus, the final study population consisted of 4,867 men (Supplementary Fig. 1). In addition, 132 women recruited between 25 January 1977 and 6 January 1984 underwent baseline OGTT. One was excluded owing to known diabetes and 3 owing to emigration, but none of them underwent intervention, leaving a total of 128 female subjects. The Malmö Preventive Project was approved by the ethics committee of Lund University and conducted in accordance with the Declaration of Helsinki. All participants gave informed consent.

Baseline Variables

Participants used a self-administered questionnaire to provide information on lifestyle and medical history, including a history of diabetes in first-degree relatives, cardiovascular disease, and current medication. Prevalent diabetes was defined as self-reported diabetes or according to the 1985 World Health Organization criteria (24). Blood glucose and serum lipids were obtained after an overnight (≥10 h) fast. Blood glucose was analyzed using the glucose oxidase (1974–1977) or the hexokinase (1977–1992) method. Serum lipids were analyzed using the local laboratory’s standard methods. A 2-h OGTT was performed by ingestion of 30 g glucose/m² body surface area (DuBois formula), with glucose levels determined at 0, 20, 40, 60, 90, and 120 min (25). Analyses of postload glucose levels were focused on measurements at 1 h and 2 h.

Outcomes

We used national and local registries to record clinical end points. Besides the diagnosis itself, the date of diagnosis is also coded in these registries. All events (type 2 diabetes, myocardial infarction, diabetic retinopathy, and diabetes with peripheral vascular complications, including ulcer) were defined according to the relevant ICD-7 to ICD-10 codes (Supplementary Table 1). Reported validities in the Swedish National Inpatient Register were high for all diagnoses (26). Mortality follow-up was based on the national registry on causes of mortality at the Swedish Central Bureau of Statistics. As follow-up was limited to 31 December 2013, the potential minimum and maximum follow-up times were 35 and 39 years, respectively.

Statistical Methods

Continuous variables are presented as mean ± SD (normally distributed variables) or median (interquartile range [IQR]) (non–normally distributed variables). Categorical variables are presented as counts and corresponding percentages. Kaplan-Meier analysis with the log-rank test and Cox proportional hazards regression with Harrell concordance index (C index), assuming an uncensored policy for handling ties, were used for assessment of discriminative ability for postload glucose measurements, including comparisons between predefined risk groups (27). Hazard ratios (HRs) were reported unadjusted and adjusted for age, BMI, IFG, triglycerides, and family history of diabetes. Furthermore, the ability of 1-h and 2-h postload glucose measurements to enhance prognostication in addition to fasting blood glucose was tested with categorical net reclassification improvement (28). All glucose measurements were assessed in a binary fashion, using the following cut points: IFG, fasting blood glucose ≥5.6 mmol/L (100 mg/dL); 1-h glucose, ≥8.6 mmol/L (155 mg/dL); and IGT, 2-h BG ≥7.8 mmol/L (140 mg/dL) (7,10). Analyses were performed at 12 years and at maximal available follow-up, respectively. This was because of the possibility of the intervention among high-risk individuals during the first 12 years after recruitment affecting the study outcomes because even though we attempted to minimize the implications of the intervention by excluding individuals who were subjected to it, there may have been a spillover effect to the control subjects, given the population-based nature of the study. Results obtained from the women were reported separately. Therefore, unless explicitly stated otherwise, all analyses and conclusions were based on the larger male population. The significance level was 5% (two sided), and no adjustments for multiple comparisons were made, as the study was considered exploratory. All analyses were performed with IBM SPSS Statistics 23 (IBM, Armonk, NY) and Stata/IC 15 (StataCorp, College Station, TX).

RESULTS

Table 1 shows baseline anthropometric, clinical, and laboratory characteristics of the study participants. All 4,867 subjects were male, with a median age of 48 years (IQR 48–49; range 27–52), mean BMI 24.8 ± 3.1 kg/m², mean body surface area 1.93 ± 0.15 m², and mean total cholesterol level 5.8 ± 1.0 mmol/L (225 ± 40 mg/dL).
A history of a sedentary lifestyle (leisure time mostly spent on sedentary activities, including reading, television, and cinema) was reported in 2,757 (57%), and 655 (13%) had a first-degree relative with diabetes. Normal postload blood glucose levels (NGT/1h-normal) were found in 3,139 (65%), elevated glucose at 1 h only (NGT/1h-high) was found in 1,564 (32%), and IGT only (IGT/1h-normal) was found in 32 (1%), and 132 (3%) had both elevated 1-h glucose and IGT (IGT/1h-high). Collectively, 1,696 (35%) individuals had elevated glucose at 1 h, and 164 (3%) had IGT. Glucose levels at 1 h and 2 h were moderately correlated (Pearson r = 0.332, P < 0.001) (Supplementary Fig. 2).

Cumulative Events
Median follow-up time was 33 years (IQR 24–37). At 12 and 39 years, 65 (1%) and 636 (13%) individuals had been diagnosed with type 2 diabetes, corresponding to incidence densities of 1.2 and 4.8 per 1,000 person-years, respectively. Cumulative incidences were lowest in subjects with NGT/1h-normal, highest in subjects with IGT/1h-high, and greater in subjects with NGT/1h-high than in those with IGT/1h-normal (Table 2 and Supplementary Table 2).

Hazard Risk
The Kaplan-Meier plot shows the unadjusted type 2 diabetes–free survival for risk categories based on postload blood glucose measurements (Fig. 1A and Supplementary Figs. 3 and 4). Congruent with the above, both crude and adjusted HRs for development of type 2 diabetes were significantly greater in risk categories including subjects with elevated 1-h blood glucose levels (Table 3 and Supplementary Table 3).

Discriminative Ability
The presence of an elevated 1-h blood glucose level was associated with significantly greater discriminative ability than IGT based on 2-h blood glucose at both 12 years (C index 0.698 vs. 0.553, P < 0.001) and 39 years (C index 0.637 vs. 0.511, P < 0.001). Additionally, the presence of IFG or elevated 1-h blood glucose was associated with a greater risk of type 2 diabetes than IFG or IGT at 12 years (HR 7.99 [95% CI 3.99–13.26], P < 0.001, C index 0.720, vs. HR 4.64 [95% CI 2.69–7.99], P < 0.001, C index 0.600; P for difference <0.001) and 39 years (HR 3.31 [95% CI 2.82–3.88], P < 0.001, C index 0.636, vs. HR 2.28 [95% CI 1.83–2.84], P < 0.001, C index 0.537; P for difference <0.001).

![Table 1—Baseline characteristics of the study population, stratified according to glycemic category](image)

<table>
<thead>
<tr>
<th>Study population</th>
<th>Total</th>
<th>NGT/1h-normal</th>
<th>NGT/1h-high</th>
<th>IGT/1h-normal</th>
<th>IGT/1h-high</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>4,867</td>
<td>3,139 (65)</td>
<td>1,564 (32)</td>
<td>32 (1)</td>
<td>132 (3)</td>
<td></td>
</tr>
<tr>
<td>Active smoking</td>
<td>48 (48–49)</td>
<td>48 (48–49)</td>
<td>48 (48–49)</td>
<td>48 (47–49)</td>
<td>48 (48–49)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>655 (13)</td>
<td>375 (12)</td>
<td>254 (16)</td>
<td>6 (19)</td>
<td>20 (15)</td>
<td>0.001b</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>2,757 (57)</td>
<td>1,740 (55)</td>
<td>914 (58)</td>
<td>26 (63)</td>
<td>83 (63)</td>
<td>0.09b</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8 ± 3.1</td>
<td>24.6 ± 3.0</td>
<td>25.1 ± 3.3</td>
<td>25.7 ± 3.6</td>
<td>25.7 ± 3.3</td>
<td>0.001c</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>130 ± 16</td>
<td>128 ± 14</td>
<td>134 ± 17</td>
<td>133 ± 19</td>
<td>143 ± 21</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>88 ± 10</td>
<td>87 ± 10</td>
<td>90 ± 10</td>
<td>90 ± 14</td>
<td>94 ± 14</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/L [mg/dL]</td>
<td>4.6 ± 0.5</td>
<td>4.5 ± 0.5</td>
<td>4.8 ± 0.5</td>
<td>4.8 ± 0.6</td>
<td>5.0 ± 0.6</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>20-min blood glucose, mmol/L [mg/dL]</td>
<td>7.6 ± 1.4</td>
<td>7.3 ± 1.3</td>
<td>8.2 ± 1.3</td>
<td>6.7 ± 1.2</td>
<td>7.9 ± 1.4</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>40-min blood glucose, mmol/L [mg/dL]</td>
<td>9.0 ± 1.8</td>
<td>8.2 ± 1.3</td>
<td>10.5 ± 1.5</td>
<td>8.0 ± 1.2</td>
<td>10.5 ± 1.6</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>1-h blood glucose, mmol/L [mg/dL]</td>
<td>8.0 ± 1.9</td>
<td>6.8 ± 1.1</td>
<td>10.0 ± 1.2</td>
<td>7.4 ± 0.7</td>
<td>11.0 ± 1.6</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>2-h blood glucose, mmol/L [mg/dL]</td>
<td>5.2 ± 1.3</td>
<td>4.9 ± 1.1</td>
<td>5.4 ± 1.2</td>
<td>8.1 ± 0.3</td>
<td>8.6 ± 0.7</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L [mg/dL]</td>
<td>5.8 ± 1.0</td>
<td>5.8 ± 1.0</td>
<td>5.9 ± 1.0</td>
<td>5.7 ± 1.0</td>
<td>6.1 ± 1.0</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>Triglycerides, mmol/L [mg/dL]</td>
<td>1.4 (1.0–1.8)</td>
<td>1.3 (1.0–1.7)</td>
<td>1.5 (1.1–2.1)</td>
<td>1.4 (1.1–2.3)</td>
<td>1.6 (1.1–2.1)</td>
<td>&lt;0.001c</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± SD (normally distributed variables: BMI, blood pressure, blood glucose, and total cholesterol) or median (IQR) (non-normally distributed variables: age and triglycerides). Data for the study population (first row) and categorical variables (active smoking, family history of diabetes, and sedentary lifestyle) are presented as counts and corresponding percentages. *Kruskal-Wallis rank test. **Pearson χ² test. †One-way ANOVA.

![Table 2—Cumulative incidence and incidence density of type 2 diabetes, stratified according to glycemic category](image)

<table>
<thead>
<tr>
<th>Study population, n (%)</th>
<th>Total</th>
<th>NGT/1h-normal</th>
<th>NGT/1h-high</th>
<th>IGT/1h-normal</th>
<th>IGT/1h-high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes incidence, n (%)</td>
<td>4,867</td>
<td>3,139 (65)</td>
<td>1,564 (32)</td>
<td>32 (1)</td>
<td>132 (3)</td>
</tr>
<tr>
<td>12 years</td>
<td>65 (1)</td>
<td>17 (0.5)</td>
<td>39 (2)</td>
<td>0</td>
<td>9 (7)</td>
</tr>
<tr>
<td>39 years</td>
<td>636 (13)</td>
<td>259 (8)</td>
<td>343 (22)</td>
<td>4 (13)</td>
<td>30 (23)</td>
</tr>
<tr>
<td>Type 2 diabetes incidence density, per 1,000 person-years</td>
<td>12 years</td>
<td>1.2</td>
<td>0.5</td>
<td>2.2</td>
<td>0</td>
</tr>
<tr>
<td>39 years</td>
<td>4.8</td>
<td>2.9</td>
<td>8.8</td>
<td>4.4</td>
<td>9.6</td>
</tr>
</tbody>
</table>
Reclassification

The abilities of elevated 1-h and 2-h blood glucose levels to reclassify risk in addition to fasting blood glucose measurements were tested in separate models. Two risk categories were applied, and reclassification could only be present if postload glucose levels were elevated in subjects with normal fasting glucose. As such, the addition of 1-h glucose was associated with greater net reclassification improvement than the addition of 2-h glucose at both 12 years (0.308 vs. 0.066) and 39 years (0.214 vs. 0.016) (Supplementary Table 4).

Glucose Measurements at Earlier Time Points

To highlight the importance of 1-h blood glucose measurements, we performed supplemental analyses comparing glucose levels obtained at 20 and 40 min with those obtained at fasting, 1 h, and 2 h in predicting incident type 2 diabetes and all-cause mortality (Supplementary Tables 8 and 9). Standardized HRs for glucose measurements obtained at time points earlier than 2 h were generally greater among the younger and thinner halves of the study population, but only the interaction terms between BMI and 40-min and 1-h glucose, and between age and 40-min glucose, were statistically significant (Supplementary Table 10).

Female Subjects

Median age at baseline was 39 years (IQR 38–40; range 29–56). Median follow-up was 36 years (IQR 35–36). Mean blood glucose concentrations were 4.7 ± 0.5 mmol/L (84 ± 8 mg/dL) at fasting, 7.5 ± 1.9 mmol/L (135 ± 34 mg/dL) at 1 h, and 5.8 ± 1.2 mmol/L (104 ± 22 mg/dL) at 2 h. Four (3%) had an elevated 2-h glucose concentration, and 41 (32%) had an elevated level at 1 h. Accordingly, 86 (67%) were categorized as NGT/1h-normal, 38 (30%) were categorized as NGT/1h-high, 1 (1%) was categorized as IGT/1h-normal, and 3 (2%) were categorized as IGT/1h-high. None had developed type 2 diabetes at 12 years. At complete follow-up, 13 (10%) had been diagnosed with type 2 diabetes, corresponding to an incidence density of 3.2/1,000 person-years. Cumulative incidences (and incidence densities per 1,000 person-years) in the four categories were 8% (2.5), 13% (4.2), 0% (0), and 33% (13.6), respectively. Compared with the NGT/1h-normal group, HRs were 1.72 (95 CI 0.55–5.43), P = 0.35, for the NGT/1h-high

Figure 1—A: Kaplan-Meier plot showing unadjusted risk of type 2 diabetes. B: Kaplan-Meier plot showing unadjusted survival.
Table 3—Crude and adjusted HRs for incident type 2 diabetes and all-cause mortality, stratified according to glycemic category

<table>
<thead>
<tr>
<th>Risk groupa</th>
<th>Crude HR (95% CI)</th>
<th>P</th>
<th>Adjusted HR (95% CI)b</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT/1h-high</td>
<td>4.75 (2.69–8.93)</td>
<td>&lt;0.001</td>
<td>3.87 (2.16–6.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGT/1h-normalf</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT/1h-high</td>
<td>13.76 (6.13–30.87)</td>
<td>&lt;0.001</td>
<td>9.00 (3.83–21.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>39 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT/1h-high</td>
<td>3.39 (2.88–3.99)</td>
<td>&lt;0.001</td>
<td>2.93 (2.48–3.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGT/1h-normal</td>
<td>1.56 (0.58–4.18)</td>
<td>0.38</td>
<td>1.17 (0.43–3.15)</td>
<td>0.76</td>
</tr>
<tr>
<td>IGT/1h-high</td>
<td>3.71 (2.54–5.41)</td>
<td>&lt;0.001</td>
<td>2.76 (1.87–4.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT/1h-high</td>
<td>1.41 (1.13–1.75)</td>
<td>0.002</td>
<td>1.35 (1.07–1.69)</td>
<td>0.01</td>
</tr>
<tr>
<td>IGT/1h-normal</td>
<td>1.57 (0.50–4.90)</td>
<td>0.44</td>
<td>1.42 (0.45–4.45)</td>
<td>0.55</td>
</tr>
<tr>
<td>IGT/1h-high</td>
<td>1.77 (1.03–3.05)</td>
<td>0.04</td>
<td>1.58 (0.91–2.74)</td>
<td>0.11</td>
</tr>
<tr>
<td>39 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT/1h-high</td>
<td>1.29 (1.19–1.39)</td>
<td>&lt;0.001</td>
<td>1.29 (1.19–1.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGT/1h-normal</td>
<td>0.81 (0.49–1.32)</td>
<td>0.39</td>
<td>0.80 (0.49–1.31)</td>
<td>0.38</td>
</tr>
<tr>
<td>IGT/1h-high</td>
<td>1.30 (1.05–1.60)</td>
<td>0.02</td>
<td>1.27 (1.02–1.57)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

aThe NGT/1h-normal group serves as baseline (comparator group). bThe multivariable Cox proportional hazards regression model was adjusted for age, BMI, IFG, triglycerides, and family history of diabetes. cThere were no events in this small group at 12 years.

The ability of 1-h blood glucose levels to predict diabetes complications and mortality is less well studied. Elevated glucose levels at 1 h are associated with adverse metabolic and cardiovascular changes, reflected by body composition, cholesterol levels, and subclinical target organ damage, including arterial stiffness, carotid intima-media thickness, and left ventricular hypertrophy (19,20,29–31). However, very few reports of the clinical consequences have been published (32–35), and although associations with macrovascular events and mortality have been shown, only one study of 1,945 subjects included glucose levels at 2 h and indicated that 1-h glucose levels predicted all-cause mortality among subjects with NGT (35). Our study demonstrates for the first time an association between elevated 1-h blood glucose levels and adverse cardiovascular prognosis, including microvascular complications, in subjects with NGT, while at the same time showing the lack of such an association in subjects with IGT only. Furthermore, the 1-h blood glucose level predicted mortality, whereas isolated IGT did not.

Although the 2-h OGTT has received less emphasis by the American Diabetes Association (8), the majority of evidence for intervention among subjects with prediabetes comes from studies of overweight or obese individuals with IGT (3–6). Furthermore, both fasting glucose and HbA1c have limited sensitivity and specificity for detecting subjects at risk, especially because of high false-negative rates, and the current study provides evidence that the 1-h OGTT is superior to fasting glucose alone for identifying high-risk subjects (7,10,12,13,15,16,36–38). Hence, a more sensitive strategy is needed, which at the same time is simple to use in a primary care setting and less time consuming and more convenient than the 2-h OGTT.

The current study extends the results from a previous report from the Malmö Preventive Project and shows that the 1-h time limit provides not only the best compromise in terms of time consumption (performs equivalent to or better than glucose measurement at 90 min) but also prognostic ability (performing better than glucose measurements at 20 and 40 min) (17). The proposed cut point for 1-h blood glucose identifies a substantially larger proportion of subjects at high risk compared with conventional IGT (10,12,13), and its use could lead to more widespread preventive efforts. However, since subjects for whom screening for type 2 diabetes is recommended already have an adverse risk profile (7,8), using a 1-h OGTT should lead to a reduced burden of both diabetes and its complications, without an excess risk of harm.

The pathophysiological significance of elevated 1-h blood glucose levels is not
fully understood. Proposely, these individuals may be at an intermediate stage between NGT and IGT or represent a phenotype distinct from that of individuals with IGT (10,19,20). In subjects with NGT, an elevated 1-h glucose level is associated with insulin resistance to a degree similar to that seen among individuals with IGT. Insulin secretion is also affected, albeit to a lesser extent (19,20). Furthermore, the risk of future type 2 diabetes associated with elevated 1-h blood glucose levels was temporally persistent but greater in the IGT/1h-high group than in the NGT/1h-normal group, particularly at shorter follow-up. These findings, in addition to those stated above, largely support the first theory and further support the concept that worsening β-cell function, not insulin resistance, is the main culprit involved in progressive glucometabolic deterioration (13).

Our results highlight the potential benefit of targeting individuals with an elevated 1-h blood glucose level and provide a strong rationale for an interventional study in which subjects are selected based on this abnormality. Should preventive efforts prove beneficial in this relatively large group, it would become prudent to consider 1-h blood glucose as a replacement for 2-h blood glucose.

A few limitations deserve mention. The definition of type 2 diabetes has changed over the past decades, notably with the lowering of the fasting glucose threshold in 1997 and the introduction of HbA1c-defined diabetes in 2011 (7). However, despite there being only a partial overlap between subjects with prediabetes and diabetes defined according to these different measures, the predictive capability of clinical risk factors remains comparable (7,39). The 30 g/m² glucose load was the standard procedure at the initiation of the study, and based on estimates of body surface area, this resulted in an average glucose load 23% lower than with the use of 75-g glucose. Prior studies have suggested that a larger glucose load results in greater differences in glucose concentrations at 2 h than at 1 h. In individuals without IGT or diabetes, the glucose levels at 1 h are virtually identical when comparing a 50-g with a 100-g glucose load. Even at 2 h, the difference appears to be small, with highly correlated values (40–43). Discrepancies between glucose levels are larger among subjects with IGT at both 1 h and 2 h (42). Theoretically, the lower glucose dose might have had a slightly greater impact on the 2-h level than the 1-h level, improving the relative sensitivity of the 1-h measurement, but significant differences have not been shown for 75 g versus 100 g, and it is not likely that important differences would exist for the glucose load used in our study compared with the standard 75-g load (43). In contrast with the well-established partitions for fasting glucose and 2-h OGTT, the cut point of 8.6 mmol/L for 1-h OGTT has been less thoroughly investigated and was derived from the San Antonio Heart Study (10). However, use of a cut point derived from our own cohort would have inflated its utility compared with 2-h OGTT. An additional limitation might be attributed to the use of two different approaches for measurement of glucose levels, although the glucose oxidase and hexokinase methods have been shown to deliver well-correlated results (44). The generalizability of our results beyond white men may be limited, but there is no evidence to suggest sex- or race-related differences in the prognostic ability of 1-h versus 2-h OGTT. However, women may have slightly lower mean concentrations of 1-h glucose, with a slower return to baseline levels (45). This fits well with the observation that traditionally defined IGT is more prevalent in females than in males (9). Most women were recruited later during the Malmö Preventive Project, when routine performance of the comprehensive OGTT had been omitted owing to financial restrictions. Thus, very few women underwent such testing and the results obtained from this subgroup should be interpreted very cautiously, given the minuscule number of events. The isolated IGT group was small, and although results were consistent, CIs were wide. Still, this finding by itself is valuable, as it indicates a minimal loss by not capturing these individuals. Finally, although we excluded the individuals who underwent lifestyle intervention to enhance the interpretability of our study, this might have resulted in removal of the subjects who had the highest a priori risk for type 2 diabetes and associated complications, underestimating the true incidence of outcomes, particularly in the subgroups with abnormal baseline glycemic status.

In conclusion, the 1-h blood glucose level is a powerful predictor of future type 2 diabetes, with net reclassification improvement and detection rates significantly greater than 2-h blood glucose measurements, especially with longer duration of follow-up. The 1-h blood glucose level is further associated with diabetes complications and mortality. Finally, simple logistics favor the use of a 1-h versus a 2-h OGTT. Therefore, 1-h blood glucose should be considered as a replacement for 2-h blood glucose as the preferred marker of IGT.

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References
28. Maki DG. Review: HbA1c has low accuracy for prediabetes; lifestyle programs and metformin reduce progression to T2DM. Ann Intern Med 2017;166:JC41
32. Maki DG. Review: HbA1c has low accuracy for prediabetes; lifestyle programs and metformin reduce progression to T2DM. Ann Intern Med 2017;166:JC41
34. Siik CW, Burnham CE, Stewart J, McDonald GW. Comparison of the 50 and 100 gram oral glucose tolerance test. Diabetes 1970;19:852–862
35. National Center for Health Statistics. The one-hour oral glucose tolerance test. Response of middle-aged men to 100-gram and 50-gram doses of glucose given fasting and 1, 2, and 3 hours after meal. Vital Health Stat 1973;2:1–34
36. de Nobel E, van’t Laar A. The size of the loading dose as an important determinant of the re- sults of the oral glucose tolerance test: a study in subjects with slightly impaired glucose tolerance. Diabetes 1978;27:42–48
41. Maki DG. Review: HbA1c has low accuracy for prediabetes; lifestyle programs and metformin reduce progression to T2DM. Ann Intern Med 2017;166:JC41
42. de Nobel E, van’t Laar A. The size of the loading dose as an important determinant of the re- sults of the oral glucose tolerance test: a study in subjects with slightly impaired glucose tolerance. Diabetes 1978;27:42–48
45. Sayetta RB, Murphy RS. Summary of current diabetes-related data from the National Center for Health Statistics. Diabetes Care 1979;2:105–119