Postchallenge Plasma Glucose and Glycemic Spikes Are More Strongly Associated With Atherosclerosis Than Fasting Glucose or HbA$_1c$ Level

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OBJECTIVE — To observe the relationship of fasting plasma glucose (FPG), postchallenge plasma glucose (PG) (30, 60, 90, and 120 min during an oral glucose tolerance test [OGTT]), as well as maximal PG during an OGTT, postchallenge glucose spikes [PGS], and glucose under the OGTT curve), and HbA$_1c$ to intima-media thickness (IMT) as a marker of atherosclerosis.

RESEARCH DESIGN AND METHODS — OGTT, ultrasound measurement of carotid IMT, and various atherosclerosis risk factors, such as family history of diabetes, obesity, and/or hyperlipoproteinemia, but without known diabetes, were analyzed in 582 individuals aged 40–70 years and at risk for type 2 diabetes.

RESULTS — In univariate analysis, all examined glycemic parameters were significantly correlated to IMT. The 2-h postchallenge plasma glucose showed the strongest odds ratio (OR) of 1.88 (1.34–2.63) in relation to abnormal IMT. All PG variables, except for FPG during OGTT, showed a significant OR, whereas the OR for HbA$_1c$ and FPG was not significant. In logistic regression analysis, 2-h PG was identified as the strongest determinant of IMT from all glycemic parameters. The 2-h PG and PGS, but not FPG, were associated with a significant rise of IMT in tertiles of HbA$_1c$. Glycemic parameters were strongly related to each other and to many atherosclerosis risk factors. In multivariate analysis including a variety of atherosclerosis risk factors, 2-h PG was a significant independent determinant of IMT.

CONCLUSIONS — PG and PGS are more strongly associated with carotid IMT than FPG and HbA$_1c$ level and modify substantially the risk for atherosclerosis, estimated by HbA$_1c$ alone, in a cohort at risk for diabetes and in the early diabetes stage.

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Macrovascular disease is the most important cause of mortality and morbidity in individuals with type 2 diabetes (1). Even when adjusted for conventional risk factors, diabetic individuals still exhibit a two- to fourfold increased risk in comparison with nondiabetic subjects (2). Therefore, hyperglycemia is supposed to exert a harmful effect on the arterial wall and has recently been a focus of keen research. High blood glucose concentration was shown to be a risk factor for mortality, even in nondiabetic individuals (3). Although the relevance of glycemic exposure is indisputable, fasting plasma glucose (FPG) and HbA$_1c$, the most commonly measured glycemic parameters, do not completely explain the risk. Recently, the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study demonstrated that “fasting glucose concentrations alone do not identify individuals at increased risk of death associated with hyperglycemia” and that “the oral glucose tolerance test provides additional prognostic information” (4). In addition, the Diabetes Control and Complications Trial group suggested that “mean HbA$_1c$ is not the most complete expression of the degree of glycemia. Other features of diabetic glucose control, which are not reflected by HbA$_1c$, may add to or modify the risk of complications. For example, the risk of complications may be more highly dependent on the extent of postprandial glycemic excursions” (5). This question was further extended from micro- to macrovascular complications (6). Although there is increasing evidence that postprandial hyperglycemia, which is not inevitably reflected by HbA$_1c$, is a strong risk factor for the development of macrovascular complications in diabetes (7–10), and even in impaired glucose tolerance (IGT) (3,11), it is not a generally accepted risk factor (12). Many of the studies reported so far lack either postchallenge plasma glucose (PG) or FPG concentrations (12). Furthermore, taking into account that the marked postprandial rise in blood glucose is a typical event in diabetes, it is surprising how little is known about the postprandial glycemic spikes as a possible contributor to atherosclerosis. Therefore, we examined the relationship of a variety of glycemic parameters—FPG and PG (30, 60, 90, and 120 min during an oral glucose tolerance test [OGTT] as well as maximal PG during OGTT, postchallenge glucose spikes [PGS], and glucose under the OGTT curve) and HbA$_1c$ to carotid intima-media thickness (IMT) of the common carotid artery (CCA), which is a generally accepted marker of atherosclerosis (13–17). The measurement of IMT, as originally described by Pignoli et al.
normal glucose tolerance (NGT); †
asked to abstain from heavy exercise or

tics of the examined subjects are shown
medication affecting glucose tolerance
lipoproteinemia. Known diabetes and
diabetes, such as family history of type 2
jects (40–70 years of age) were examined
ously published (11,19,22). In brief, sub-
Details on study design have been previ-
Atherosclerosis and Diabetes Study .
this question in subjects in the early stages of
betes and even in IGT (19–21), we analyzed
consistently increased in newly detected dia-
disease starts ticking before the clinical onset
out clinical cardiovascular disease (CVD)
infarction and stroke even in subjects with-
to be a strong predictor for myocardial
occurrence of macrovascular disease
(sclerosis (14,15). IMT of the CCA was shown to
noninvasive method to monitor atheroscle-
(13), is a highly reproducible and suitable
noninvasive method to monitor atheroscle-
tional methods, as already published

RESEARCH DESIGN AND
METHODS — A total of 582 subjects
were analyzed who were consecutive par-
ticipants of the Risk Factors in IGT for
Atherosclerosis and Diabetes Study. Details on study design have been previ-
ously published (11,19,22). In brief, sub-
jects (40–70 years of age) were examined
who were at risk for the development of
diabetes, such as family history of type 2
diabetes, obesity, and/or hyper- or dys-
lipoproteinemia. Known diabetes and
medication affecting glucose tolerance
were exclusion criteria. Basic characteris-
tics of the examined subjects are shown in Table 1.

The analysis was conducted following
a strict protocol. All participants were
asked to abstain from heavy exercise or
sedentary behavior as well as from food
excess or hunger for 3 days before the test.
Venous blood was drawn after an
overnight fast of at least 10 h. OGTT was
performed with 75 g glucose (Glucohex;
Roche, Reutlingen, Germany), and blood
was collected for the measurement of
plasma glucose every 30 min for 2 h. The
PGS were defined as the difference
between the maximal PG level during
OGTT, irrespective of the time after glu-
cose challenge, and the level of FPG.

### Table 1—Characteristics of the examined subjects (n = 582) in stages of glucose tolerance

<table>
<thead>
<tr>
<th></th>
<th>NGT</th>
<th>IGT</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.6 ± 0.5</td>
<td>55.2 ± 0.6</td>
<td>57.0 ± 0.87*</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>148/184</td>
<td>78/92</td>
<td>52/28</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 ± 0.2</td>
<td>28.2 ± 0.3*</td>
<td>29.0 ± 0.5*</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.87 ± 0.005</td>
<td>0.91 ± 0.007*</td>
<td>0.95 ± 0.011†</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133.2 ± 1.0</td>
<td>137.6 ± 1.4*</td>
<td>139.9 ± 2.1*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82.6 ± 0.6</td>
<td>85.7 ± 0.7*</td>
<td>85.8 ± 1.1*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.80 ± 0.06</td>
<td>5.87 ± 0.08</td>
<td>5.98 ± 0.1</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.43 ± 0.05</td>
<td>2.06 ± 0.1*</td>
<td>3.04 ± 0.4*†</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.52 ± 0.02</td>
<td>1.36 ± 0.03*</td>
<td>1.27 ± 0.04*</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>5.45 ± 0.02</td>
<td>5.67 ± 0.04*</td>
<td>6.24 ± 0.08*†</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.64 ± 0.02</td>
<td>6.08 ± 0.04*</td>
<td>7.32 ± 0.11†</td>
</tr>
<tr>
<td>2-h postprandial plasma glucose (mmol/l)</td>
<td>5.85 ± 0.06</td>
<td>8.99 ± 0.08*</td>
<td>11.66 ± 0.44†</td>
</tr>
<tr>
<td>PGS spikes (mmol/l)</td>
<td>3.76 ± 0.09</td>
<td>5.78 ± 0.1*</td>
<td>7.39 ± 0.2*†</td>
</tr>
<tr>
<td>Family history of diabetes (%)</td>
<td>57</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>13</td>
<td>26*</td>
<td>32*</td>
</tr>
</tbody>
</table>

Data are n, means ± SEM, or % and are based on the new diagnostic criteria for diabetes (23). *P < 0.05 vs. normal glucose tolerance (NGT); †P < 0.05 vs. IGT. Obesity = BMI ≥ 30 kg/m².

### Table 2—Correlation of FPG, PG in a 75-g OGTT, and HbA₁c to IMT, and glycemic parameters in relation to abnormal IMT

<table>
<thead>
<tr>
<th>FPG</th>
<th>Unadjusted Age/sex-adjusted</th>
<th>OR (95% CI) in relation to abnormal IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.167*</td>
<td>0.10*</td>
<td>1.30 (0.92–1.82)</td>
</tr>
</tbody>
</table>

Univariate and partial correlation after age and sex adjustment to IMT

Ultrasound measurement
B-mode ultrasound of the CCA was per-
formed with an Acuson 128XP computed
sonography system using a 10-MHz linear
array transducer, as published elsewhere
(11,19,22). In brief, the thickness of the
intima-media complex was assessed as
described by Pignoli et al. (13). Measure-
ments were conducted in plaque-free por-
tions of the 10-mm linear segment proximal
to the carotid bulb. For each patient, two
measurements were performed bilaterally
and the values averaged. The ultrasound
examination was conducted on the day of
blood collection for laboratory analysis, so
that both study participants and physicians
were unaware of the corresponding labora-
tory values. The reproducibility of the IMT
measurement was found to be good, as pre-
viously published (22).

### Laboratory examination
Venous blood was collected in EDTA
monovettes, and plasma was immediately
separated by centrifugation (4,000 rpm
for 8 min at 4°C). Plasma glucose and
HbA₁c were determined using fresh mate-
rial. HbA₁c was examined by high-perfor-
mance liquid chromatography on a
Diamat Analyser (Bio-Rad, München, Ger-
many). Plasma glucose was measured by
the hexokinase method (interassay coeffi-
cient of variation = 1.5%). Plasma lipids,
coaulation and fibrinolysis parameters,
and albuminuria were determined by rou-
tine methods, as already published.
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(11,19,22). Proinsulin was analyzed by highly specific enzyme immunoassay (DGR, Marburg, Germany).

Statistics
Data evaluation was conducted using the SPSS/PC program. The distribution of values was assessed by the Kolmogorov-Smirnov test for homogeneity of variances, and the Mann-Whitney U test was performed if necessary. The level of significance was determined by $P < 0.05$. Data are presented as means and SEM. The correlation of glycemic parameters to IMT and to atherosclerosis risk factors was assessed using Pearson or Spearman correlation coefficients, as appropriate. In addition, partial correlation after adjustment for age and sex was evaluated. Odds ratios (ORs) with 95% CI were given for the glycemic variables in relation to abnormal IMT. Logistic regression analysis was applied to identify the strongest determinant of IMT among the glycemic parameters. IMT was assessed in tertiles of FPG and HbA$_{1c}$, in tertiles of 2-h postchallenge plasma glucose and HbA$_{1c}$, and in tertiles of PGS and HbA$_{1c}$, and the difference in IMT in these tertiles was evaluated in trend. Multivariate analysis was conducted by stepwise multiple linear regression.

RESULTS

As shown in Table 1, subjects with IGT and diabetes exhibited significantly increased BMI, waist-to-hip ratio, blood pressure, triglycerides, HbA$_{1c}$, and FPG and PG levels and significantly decreased HDL cholesterol levels. This remained significant after age and sex adjustment.

In univariate analysis, all glycemic parameters were significantly correlated to IMT (Table 2), which remained significant after age and sex adjustment. The 2-h postchallenge plasma glucose showed the strongest OR in relation to abnormal IMT. All PG variables, except for 30-min glucose in OGTT, showed a significant OR, whereas the OR for HbA$_{1c}$ and FPG was not significant. In logistic regression analysis, 2-h PG was identified as the strongest determinant of IMT from all glycemic parameters.

In Fig. 1, we show carotid IMT in tertiles of FPG and HbA$_{1c}$, in tertiles of 2-h PG and HbA$_{1c}$, and in tertiles of PGS and HbA$_{1c}$. It is clear that PG and PGS, but not FPG, are associated with a significant rise in trend for IMT in tertiles of HbA$_{1c}$. Glycemic parameters are strongly related to each other (Table 3). PGS are more strongly related to 2-h PG than to FPG or HbA$_{1c}$. FPG, 2-h PG, PGS, and
Table 3—Correlation between FPG, PG 2 h after a 75-g OGTT (2-h PG), PGS, and HbA1c to atherosclerosis risk factors after age and sex adjustment

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>FPG</th>
<th>2-h PG</th>
<th>PGS</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>0.652*</td>
<td>0.513*</td>
<td>0.40*</td>
<td>—</td>
</tr>
<tr>
<td>FPG</td>
<td>—</td>
<td>0.622*</td>
<td>0.45*</td>
<td>0.68*</td>
</tr>
<tr>
<td>2-h PG</td>
<td>0.622*</td>
<td>—</td>
<td>0.70*</td>
<td>0.55*</td>
</tr>
<tr>
<td>BMI</td>
<td>0.316*</td>
<td>0.314*</td>
<td>0.29*</td>
<td>0.21*</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.249*</td>
<td>0.281*</td>
<td>0.30*</td>
<td>0.13*</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.165*</td>
<td>0.202*</td>
<td>0.17‡</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.149*</td>
<td>0.168*</td>
<td>0.11§</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.238*</td>
<td>0.244*</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>—1.157*</td>
<td>—2.214*</td>
<td>—2.20*</td>
<td>—0.14†</td>
</tr>
<tr>
<td>Fasting proinsulin</td>
<td>0.616*</td>
<td>0.447*</td>
<td>0.271*</td>
<td>0.532*</td>
</tr>
<tr>
<td>2-h proinsulin in OGTT</td>
<td>0.323*</td>
<td>0.353*</td>
<td>0.311*</td>
<td>0.198*</td>
</tr>
<tr>
<td>PAI (active)</td>
<td>0.290*</td>
<td>0.234*</td>
<td>0.20#</td>
<td>0.19#</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>NS</td>
<td>0.1**</td>
<td>0.20*</td>
<td>NS</td>
</tr>
<tr>
<td>von Willebrand factor</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>NS</td>
<td>0.216*</td>
<td>0.12††</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P < 0.001; †P = 0.023; ††P = 0.003; ‡P = 0.06; ||P = 0.002; |||P = 0.019; #P = 0.001; **P = 0.05; ††P = 0.04.

HbA1c are significantly correlated to a variety of atherosclerosis risk factors (Table 3), which is more strongly expressed for PG than for HbA1c and FPG.

In multivariate analysis, including only one of the examined glycemic parameters and a variety of atherosclerosis risk factors, such as age, sex, blood pressure, BMI, waist-to-hip ratio, total cholesterol, triglycerides, HDL cholesterol, proinsulin, von Willebrand factor, fibrinogen, plasminogen activator inhibitor (active), leucocytes, and albuminuria, we found that all PG variables, but not FPG and HbA1c, turned out to be significant independent determinants of carotid IMT. If all glycemic parameters were included together with the additional risk factors in stepwise regression analysis, we found 2-h PG, along with age, male sex, proinsulin, albuminuria, HDL cholesterol, and total cholesterol as significant independent determinants of IMT.

CONCLUSIONS — Hyperglycemia has been convincingly shown to be associated with CVD (1–3). Although many studies indicate the importance of postprandial glucose, the measurement of FPG and HbA1c still dominates in the assessment of glycemic level, whereas postchallenge values are often neglected (12). This could be explained with the inconvenience and costs of an OGTT. However, taking into account the data of the Rancho Bernardo study (24) (that isolated postchallenge hyperglycemia is a risk factor of CVD, especially in older women) and the findings of the DECODE study (4) (that PG provides additional prognostic information with respect to CVD), as well as the lack of evidence on the impact of PGS on atherosclerosis, it is obviously necessary to conduct a systematic evaluation of the importance of various glycemic parameters as potential CVD risk factors. Our study is the first to explore the relation between FPG and all PG values during OGTT, PGS, and HbA1c to carotid IMT. The measurement of IMT is a suitable method to directly examine the vessel wall, which is currently used as a surrogate parameter for atherosclerosis (13–17). We found that PG and PGS are more strongly associated with IMT than FPG and HbA1c level. Thus, all postchallenge glycemic parameters, except 30 min glucose during an OGTT, had a significant OR in relation to abnormal IMT (the 2-h PG having the strongest OR), whereas the OR for HbA1c and FPG was not significant. Also, in logistic regression, 2-h PG was identified as the strongest determinant of IMT. The significance of PG and especially of 2-h PG level as an independent determinant of IMT was also confirmed in multivariate analysis, including established and new risk factors for atherosclerosis. The fact that PGS, although more strongly related to IMT than FPG and HbA1c, show a weaker association with IMT than 2-h PG could be a result of the variation of FPG, which was used for the PGS calculation.

Both PGS and 2-h PG level provide additional information with respect to IMT assessed by HbA1c alone, because their increase was associated with the significant rise of IMT for a given level of HbA1c (Fig. 1).

PGS rose parallel to the glucose intolerance stage, twice as high in newly detected diabetes than in normal glucose tolerance. This indicates a narrow range of plasma glucose in nondiabetic individuals, which is compatible with previous suggestions (25). PG significantly correlates to a variety of atherosclerosis risk factors, which is consistent with reports about coagulation activation in experimental acute hyperglycemia (6). It has been shown in diabetic individuals that hyperglycemia after normal meals causes an overproduction of free radicals and thrombin proportional to the blood glucose level (26,27). The concept of postchallenge glucose spikes introduces the possible role of glucose instability as a risk factor for atherosclerosis. Thus, it was shown that instability of FPG is a predictor of CVD mortality in type 2 diabetes (28).

In our study, in univariate analysis, all glycemic parameters significantly correlated with IMT and CVD risk factors. Moreover, these variables were strongly interrelated, which is compatible with other data (29). HbA1c was a better reflector of fasting, as was PGS of postchallenge glycemic control in this population at risk for diabetes. This differs from reports about clinical type 2 diabetes, where postprandial hyperglycemia was shown to be a better contributor to HbA1c than FPG (30). Although HbA1c, FPG, and PG are closely correlated, values that do not match are not rare (29,30). Therefore, to achieve a better estimation of the risk associated with glycemic level with respect to atherosclerosis, the whole glycemic triad—FPG, PG, and HbA1c—should be considered, especially in the prediabetic and early diabetic stage.

In conclusion, our data indicate that PG and PGS are more strongly associated with carotid IMT than FPG and HbA1c level and modify substantially the risk for atherosclerosis, estimated by HbA1c alone, in a cohort at risk for diabetes and in the early diabetic stages.

References
2. Stamler J, Vaccaro O, Neaton J, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group: Diabetes, other risk factors, and 12-year cardiovascular mortal-
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