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 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. 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.

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Abbreviations: CCA, common carotid artery; CVD, cardiovascular disease; DECODE, Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; IMT, intima-media thickness; OGTT, oral glucose tolerance test; OR, odds ratio; PG, postchallenge plasma glucose; PGS, postchallenge glucose spikes.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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

	NGT	IGT	Diabetes
Age (years)	54.6 ± 0.5	55.2 ± 0.6	57.0 ± 0.87*
Sex (M/F)	148/184	78/92	52/28*†
BMI (kg/m^2)	26.0 ± 0.2	28.2 ± 0.3*	29.0 ± 0.5*
Waist-to-hip ratio	0.87 ± 0.005	0.91 ± 0.007*	0.95 ± 0.01*†
Systolic blood pressure (mmHg)	132.3 ± 1.0	137.6 ± 1.4*	139.9 ± 2.1*
Diastolic blood pressure (mmHg)	82.6 ± 0.6	85.1 ± 0.7*	85.8 ± 1.1*
Total cholesterol (mmol/l)	5.80 ± 0.06	5.87 ± 0.08	5.98 ± 0.1
Triglycerides (mmol/l)	1.43 ± 0.05	2.06 ± 0.1*	3.04 ± 0.4*†
HDL cholesterol (mmol/l)	1.52 ± 0.02	1.36 ± 0.03*	1.27 ± 0.04*
HbA_{1c} (%)	5.45 ± 0.02	5.67 ± 0.04*	6.24 ± 0.08*†
Fasting plasma glucose (mmol/l)	5.64 ± 0.02	6.08 ± 0.04*	7.32 ± 0.1*†
2-h postprandial plasma glucose (mmol/l)	5.85 ± 0.06	8.99 ± 0.08*	11.66 ± 0.4*†
PGS spikes (mmol/l)	3.76 ± 0.09	5.78 ± 0.1*	7.39 ± 0.2*†
Family history of diabetes (%)	57	61	62
Obesity (%)	13	26*	32*

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/m^2.

(13), is a highly reproducible and suitable noninvasive method to monitor atherosclerosis (14,15). IMT of the CCA was shown to be related to cardiovascular risk factors and occurrence of macrovascular disease (16,17). Furthermore, it was recently found to be a strong predictor for myocardial infarction and stroke even in subjects without clinical cardiovascular disease (CVD) (17). Because the clock for coronary heart disease starts ticking before the clinical onset of diabetes (18), and carotid IMT is already consistently increased in newly detected diabetes and even in IGT (19–21), we analyzed this question in subjects in the early stages of the disease or at risk for diabetes.

RESEARCH DESIGN AND METHODS

— A total of 582 subjects were analyzed who were consecutive participants of the Risk Factors in IGT for Atherosclerosis and Diabetes Study. Details on study design have been previously published (11,19,22). In brief, subjects (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 dyslipoproteinemia. Known diabetes and medication affecting glucose tolerance were exclusion criteria. Basic characteristics 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 (Glucodex; Rougier, Chambly, Canada), 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 glucose challenge, and the level of FPG.

Ultrasound measurement

B-mode ultrasound of the CCA was performed with a 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). Measurements were conducted in plaque-free portions 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 laboratory values. The reproducibility of the IMT measurement was found to be good, as previously 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 HbA_{1c} were determined using fresh material. HbA_{1c} was examined by high-performance liquid chromatography on a Diamat Analyser (Bio-Rad, München, Germany). Plasma glucose was measured by the hexokinase method (interassay coefficient of variation = 1.5%). Plasma lipids, coagulation and fibrinolysis parameters, and albuminuria were determined by routine methods, as already published

Table 2—*Correlation of FPG, PG in a 75-g OGTT, and HbA_{1c} to IMT, and glycemic parameters in relation to abnormal IMT*

	Univariate and partial correlation after age and sex adjustment to IMT		OR (95% CI) in relation to abnormal IMT
	Unadjusted	Age/sex-adjusted	
FPG	0.167*	0.10†	1.30 (0.92–1.82)
PG during OGTT			
30 min	0.187*	0.112‡	1.11 (0.80–1.56)
60 min	0.228*	0.173*	1.48¶ (1.06–2.07)
90 min	0.213*	0.187*	1.45¶ (1.03–2.02)
2 h	0.214*	0.211*	1.88¶ (1.34–2.63)
Maximal	0.224*	0.168*	1.47¶ (1.05–2.05)
Spikes	0.207*	0.168*	1.50¶ (1.08–2.10)
AUC	0.232*	0.174*	1.63¶ (1.16–2.29)
HbA_{1c}	0.218*	0.123§	1.24 (0.82–1.89)

*$P < 0.001$; †$P = 0.015$; ‡$P = 0.007$; §$P = 0.003$; ¶$P < 0.05$. Cutoff limits for the ORs: fasting PG abnormal ≥6.1 mmol; PG 2 h during OGTT abnormal ≥7.8 mmol/l, based on the new diagnostic criteria for glucose intolerance (23); HbA_{1c} abnormal ≥6.1%, based on the reference values of our laboratory; for PG 30, 60, and 90 min during OGTT, as well as for PG maximal, spikes, and AUC during OGTT, the values above the 75th percentile in the group with normal glucose tolerance (*n* = 332) were determined as abnormal; IMT abnormal >1.0 mm for men and women >55 years, and IMT abnormal >0.85 mm for women <55 years.

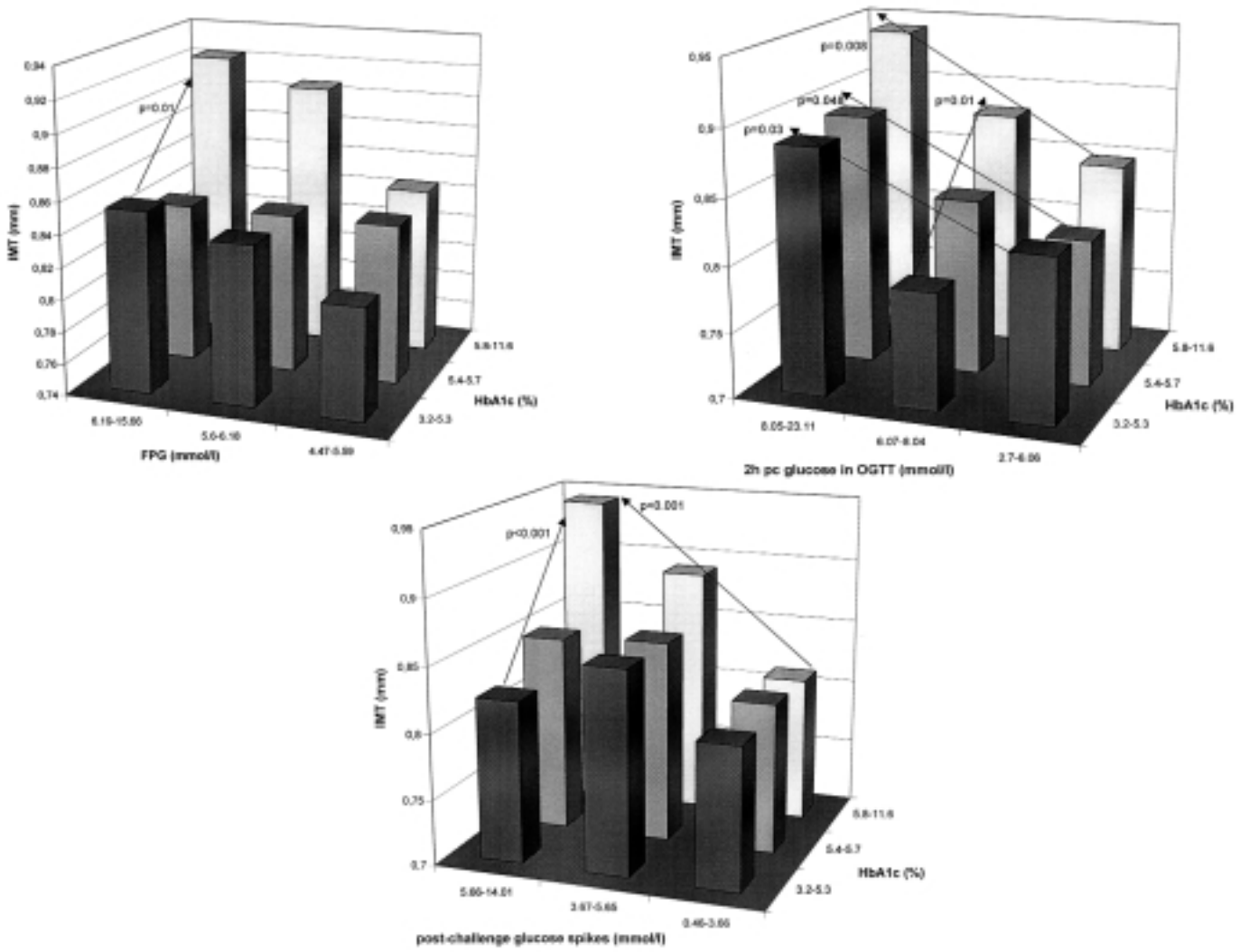

Figure 1—*Carotid IMT (in millimeters) in tertiles of FPG and HbA_{1c}, in tertiles of 2-h PG in OGTT, and HbA_{1c} and in tertiles of PGS and HbA_{1c}.*

(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 HbA_{1c} to atherosclerosis risk factors after age and sex adjustment*

	FPG	2-h PG	PGS	HbA_{1c}
HbA_{1c}	0.652*	0.513*	0.40*	—
FPG	—	0.622*	0.45*	0.68*
2-h PG	0.622*	—	0.70*	0.55*
BMI	0.316*	0.314*	0.29*	0.21*
Waist-to-hip ratio	0.249*	0.281*	0.30*	0.13†
Systolic blood pressure	0.165*	0.202*	0.17‡	NS
Diastolic blood pressure	0.149*	0.168*	0.11§	NS
Total cholestetrol	NS	NS	NS	NS
Triglycerides	0.238*	0.244*	0.17‖	NS
HDL cholesterol	−0.157*	−0.214*	−0.20*	−0.13¶
Fasting proinsulin	0.616*	0.447*	0.271*	0.532*
2-h proinsulin in OGTT	0.323*	0.353*	0.311*	0.198*
PAI (active)	0.290*	0.234*	0.20#	0.19#
Fibrinogen	NS	0.1**	0.20*	NS
von Willebrandt factor	NS	NS	NS	NS
Albuminuria	NS	0.216*	0.12††	NS

*$P < 0.001$; †$P = 0.023$; ‡$P = 0.003$; §$P = 0.06$; ‖$P = 0.002$; ¶$P = 0.019$; #$P = 0.001$; **$P = 0.05$; ††$P = 0.04$. PAI, plasminogen activator inhibitor.

HbA_{1c} are significantly correlated to a variety of atherosclerosis risk factors (Table 3), which is more strongly expressed for PG than for HbA_{1c} 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 HbA_{1c}, 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}, 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 HbA_{1c} alone, because their increase was associated with the significant rise of IMT for a given level of HbA_{1c} (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). HbA_{1c} 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 HbA_{1c} than FPG (30). Alhough HbA_{1c}, 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 HbA_{1c}—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 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 diabetic stages.

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