

# Postchallenge Plasma Glucose and Glycemic Spikes Are More Strongly Associated With Atherosclerosis Than Fasting Glucose or HbA<sub>1c</sub> Level

THEODORA S. TEMELKOVA-KURKTSCHIEV,  
MD, PHD  
CARSTA KOEHLER, PHD  
ELENA HENKEL, MD

WOLFGANG LEONHARDT, PHD  
KATJA FUECKER  
MARKOLF HANEFELD, MD, PHD

**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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub>. 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<sub>1c</sub> level and modify substantially the risk for atherosclerosis, estimated by HbA<sub>1c</sub> alone, in a cohort at risk for diabetes and in the early diabetes stage.

*Diabetes Care* 23:1830–1834, 2000

**M**acrovacular 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 indis-

putable, fasting plasma glucose (FPG) and HbA<sub>1c</sub>, 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<sub>1c</sub> is not the most complete expression of the degree of glycemia. Other features of diabetic glucose control, which are not reflected by HbA<sub>1c</sub>, 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<sub>1c</sub>, 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<sub>1c</sub> 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.

From the Institute for Clinical Metabolic Research, Technical University Dresden, Dresden, Germany.

Address correspondence and reprint requests to Theodora S. Temelkova-Kurktschiev, PhD, Institute for Clinical Metabolic Research, Technical University, Fetscher St. 74, 01307, Dresden, Germany.

Received for publication 3 April 2000 and accepted in revised form 21 August 2000.

**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 <sup>2</sup> )	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 <sub>1c</sub> (%)	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<sup>2</sup>.

(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.

**Table 2—Correlation of FPG, PG in a 75-g OGTT, and HbA<sub>1c</sub> 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 <sub>1c</sub>	0.218*	0.123§	1.24 (0.82–1.89)

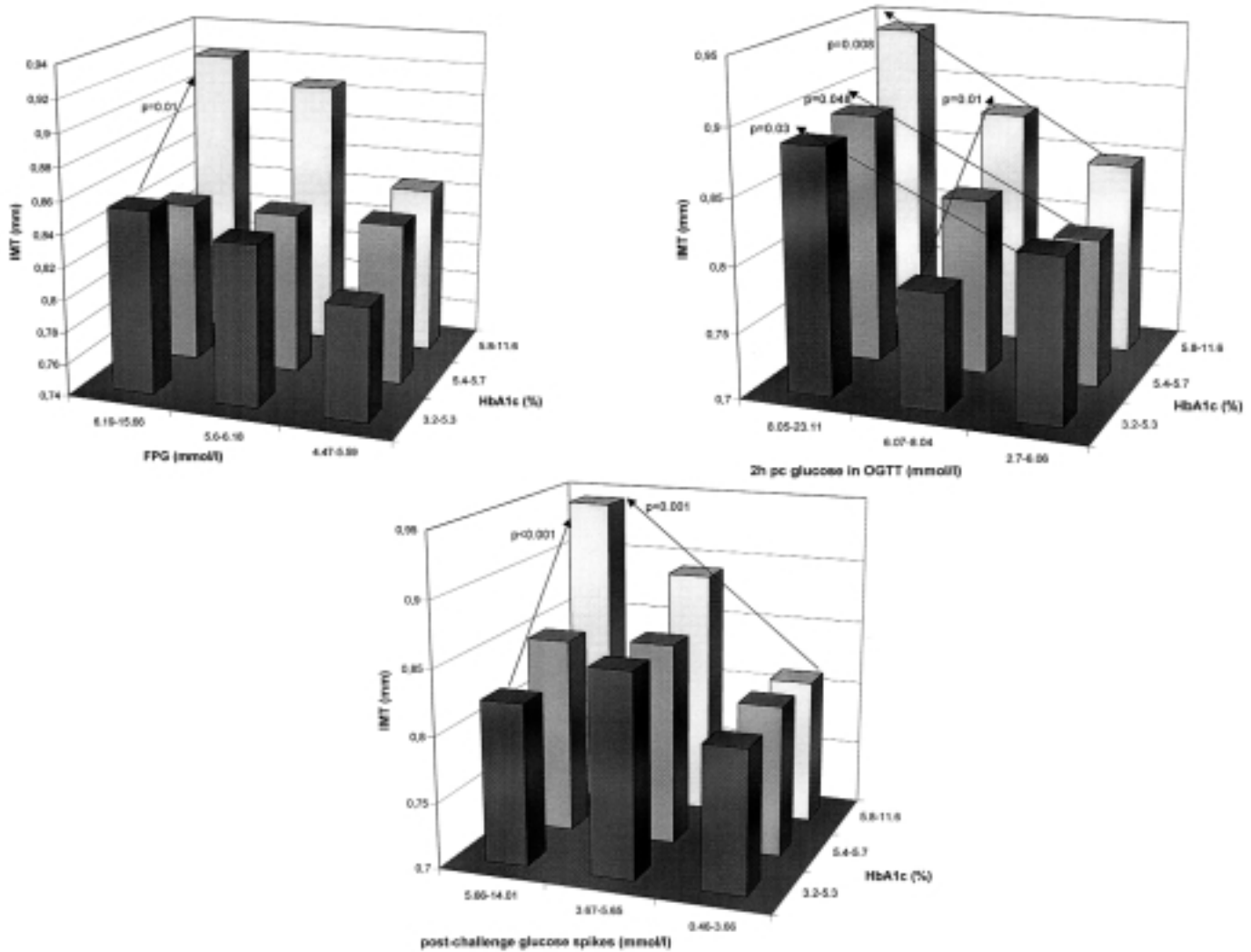
\*P < 0.001; †P = 0.015; ‡P = 0.007; §P = 0.003; ¶P < 0.05. Cutoff limits for the ORs: fasting PG abnormal ≥ 6.1 mmol; PG 2 h during OGTT abnormal ≥ 7.8 mmol/l, based on the new diagnostic criteria for glucose intolerance (23); HbA<sub>1c</sub> abnormal ≥ 6.1%, based on the reference values of our laboratory; 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.

## 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<sub>1c</sub> were determined using fresh material. HbA<sub>1c</sub> 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



**Figure 1**—Carotid IMT (in millimeters) in tertiles of FPG and HbA<sub>1c</sub>, in tertiles of 2-h PG in OGTT, and HbA<sub>1c</sub> and in tertiles of PGS and HbA<sub>1c</sub>.

(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<sub>1c</sub>, in tertiles of 2-h postchallenge plasma glucose and HbA<sub>1c</sub>, and in tertiles of PGS and HbA<sub>1c</sub>, 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<sub>1c</sub>, 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<sub>1c</sub> 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<sub>1c</sub>, in tertiles of 2-h PG and HbA<sub>1c</sub>, and in tertiles of PGS and HbA<sub>1c</sub>. It is clear that PG and PGS, but not FPG, are associated with a significant rise in trend for IMT in tertiles of HbA<sub>1c</sub>.

Glycemic parameters are strongly related to each other (Table 3). PGS are more strongly related to 2-h PG than to FPG or HbA<sub>1c</sub>. 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<sub>1c</sub> to atherosclerosis risk factors after age and sex adjustment**

	FPG	2-h PG	PGS	HbA <sub>1c</sub>
HbA <sub>1c</sub>	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 cholesterol	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<sub>1c</sub> are significantly correlated to a variety of atherosclerosis risk factors (Table 3), which is more strongly expressed for PG than for HbA<sub>1c</sub> 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<sub>1c</sub>, 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub>, 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<sub>1c</sub> alone, because their increase was associated with the significant rise of IMT for a given level of HbA<sub>1c</sub> (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<sub>1c</sub> 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<sub>1c</sub> than FPG (30). Although HbA<sub>1c</sub>, 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<sub>1c</sub>—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<sub>1c</sub> level and modify substantially the risk for atherosclerosis, estimated by HbA<sub>1c</sub> alone, in a cohort at risk for diabetes and in the early diabetic stages.

## References

- Laakso M: Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes* 48: 937–942, 1999
- 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-

- ity for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16: 434–444, 1993
3. Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyorala M, Forhan A, Eschwege E: High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 21:360–367, 1998
  4. The DECODE Study Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 354:617–621, 1999
  5. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA<sub>1c</sub>) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995
  6. Ceriello A: The emerging role of post-prandial hyperglycaemic spikes in the pathogenesis of diabetic complications. *Diabet Med* 15:188–193, 1998
  7. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelsch HJ, Lindner J, the DIS Group: Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39:1577–1583, 1996
  8. Donahue RP, Abbott RD, Reed DM, Yano K: Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry: Honolulu Heart Program. *Diabetes* 36:689–692, 1987
  9. Hanefeld M, Temelkova-Kurktschiev T: The postprandial state and the risk of atherosclerosis. *Diabet Med* 14:S6–S11, 1997
  10. Cooper R, Liu K, Stamler J, Schoenberger JA, Shekelle RB, Collette P, Shekelle S: Prevalence of diabetes/hyperglycemia and associated risk factors in blacks and whites: Chicago Heart Association Detection Project in Industry. *Am Heart J* 108:827–833, 1984
  11. Hanefeld M, Köhler C, Schaper F, Fuecker K, Henkel E, Temelkova-Kurktschiev T: Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. *Atherosclerosis* 13:7–12, 1999
  12. Groeneveld Y, Petri H, Hermans J, Springer MP: Relationship between blood glucose level and mortality in type 2 diabetes mellitus: a systematic review. *Diabet Med* 16: 2–13, 1999
  13. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R: Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 74:1399–1406, 1986
  14. Bots ML, Mulder PG, Hofman A, van Es GA, Grobbee DE: Reproducibility of carotid vessel wall thickness measurements: the Rotterdam Study. *J Clin Epidemiol* 47:921–930, 1994
  15. Persson J, Formgren J, Israelsson B, Berglund G: Ultrasound-determined intima-media thickness and atherosclerosis: direct and indirect validation. *Arterioscler Thromb* 14:261–264, 1994
  16. Salonen JT, Salonen R: Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb* 11:1245–1249, 1991
  17. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr, for the Cardiovascular Health Study Collaborative Research Group: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 340:14–22, 1999
  18. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893–2898, 1990
  19. Temelkova-Kurktschiev T, Koehler C, Leonhardt W, Schaper F, Henkel E, Siebert G, Hanefeld M: Increased intimal-medial thickness in newly detected type 2 diabetes. *Diabetes Care* 22:333–338, 1999
  20. Yamasaki Y, Kawamori R, Matsushima H, Nishizawa H, Kodama M, Kubota M, Kajimoto Y, Kamada T: Asymptomatic hyperglycemia is associated with increased intimal plus medial thickness of the carotid artery. *Diabetologia* 38:585–591, 1995
  21. Wagenknecht LE, D'Agostino RB, Haffner SM, Savage PJ, Rewers M: Impaired glucose tolerance, type 2 diabetes, and carotid wall thickness: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 21:1812–1819, 1998
  22. Temelkova-Kurktschiev T, Koehler C, Schaper F, Henkel E, Hahnefeld A, Fuecker K, Siebert G, Hanefeld M: Relationship between fasting plasma glucose, atherosclerosis risk factors and carotid intima media thickness in nondiabetic individuals. *Diabetologia* 41:706–712, 1998
  23. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
  24. Barrett-Connor E, Ferrara A: Isolated postchallenge hyperglycemia and the risk of fatal cardiovascular disease in older women and men. *Diabetes Care* 21:1236–1239, 1998
  25. Buse JB, Hroschikowski M: The case for a role for postprandial glucose monitoring in diabetes management. *J Fam Pract* 47:S29–S36, 1998
  26. Ceriello A, Toboga C, Tonutti L, Giacomello R, Stel G, Motz E, Pirizi M: Post-meal coagulation activation in diabetes mellitus: the effect of acarbose. *Diabetologia* 39:469–473, 1996
  27. Ceriello A: Acute hyperglycemia and oxidative stress generation. *Diabet Med* 14:45–50, 1997
  28. Muggeo M, Verlato G, Bonora E, Zoppini G, Corbellini M, de Marco R: Long-term instability of fasting plasma glucose, a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus: the Verona Diabetes Study. *Circulation* 96:1750–1754, 1997
  29. Bouma M, Dekker J, de Sonnaville JJ, van der Does FE, de Vries H, Kriegsman DM, Kostense PJ, van Eijk JT: How valid is fasting plasma glucose as a parameter of glycemic control on non-insulin-using patients with type 2 diabetes? *Diabetes Care* 22:904–907, 1999
  30. Avignon A, Radauceanu A, Monnier L: Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 20:1822–1826, 1997