Post-Meal Glucose Peaks at Home Associate with Carotid Intima-Media Thickness in Type 2 Diabetes

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Context: Two-hour postprandial hyperglycemia is related to chronic complications of diabetes and is currently used in the international guidelines to drive the therapy.

Objective: Our objective was to assess the size and timing of post-meal glucose peaks in the everyday life of type 2 diabetic patients and the relationship with carotid atherosclerosis.

Design, Setting, and Patients: This was an observational study performed in 644 outpatients with type 2 diabetes attending diabetes clinics located in the area of the Campania County, South Italy, who provided complete home blood glucose profiles and centralized carotid intima-media thickness (CIMT) assessment. The study was conducted from 2001–2005.

Main Outcome Measures: Incremental glucose peak (IGP) was the maximal incremental increase in blood glucose obtained at any point after the meal. CIMT was assessed by carotid sonography.

Results: The level of glycosylated hemoglobin and CIMT progressively increased across quintiles of IGP (P for trend = 0.01 for both). In univariate analysis, all examined glycemic parameters were significantly correlated with CIMT. IGP ($r = 0.40$; $P = 0.006$) showed the strongest correlation with CIMT, which remained significant in multiple linear regression analysis ($R^2 = 0.26$; $P = 0.01$). IGP was associated with a significant increase of CIMT in tertiles of glycosylated hemoglobin. IGP occurred within 1 h from the start of the meal in 95% of the entire diabetic population.

Conclusion: IGPs are frequent in the everyday life of patients with type 2 diabetes, occur for most (95%) within 1 h after meal, timing of IGPs is not influenced by treatment (diet or drugs), and IGPs correlate with CIMT. **(*J Clin Endocrinol Metab* 93: 1345–1350, 2008)**

An estimated 240 million people worldwide have diabetes, which is a leading cause of death in most developed countries (1). Large prospective studies have demonstrated that intensive treatment of hyperglycemia can significantly decrease the development and/or progression of microvascular complications of diabetes (2–5). Moreover, improvement in glycemic control significantly reduces the incidence of macrovascular events in both type 1 and type 2 diabetes (6). Until recently, the predominant focus of therapy has been on lowering glycosylated hemoglobin (HbA_{1c}) levels, with a strong emphasis on fasting plasma glucose (7). However, reducing post-meal glucose excursions is equally important (8), or perhaps more important (9–11) than simply controlling fasting plasma glucose in individuals with diabetes and impaired glucose tolerance. There is also abundant evidence for a causal relationship between acute or post-meal glucose increase and microvascular/macrovascular outcomes (12–15); moreover, there is no apparent glycemic threshold for reduction of complications (16, 17).

Two-hour postprandial and post-challenge hyperglycemia is a very frequent phenomenon in individuals with diabetes, can occur even when metabolic control appears to be adequate (18, 19), and is currently used to describe post-meal glycemic peaks. The 2-h time frame for measurement is recommended because it conforms to glucose guidelines published by most of the leading

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Abbreviations: BMI, Body mass index; CIMT, carotid intima-media thickness; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; IGP, incremental glucose peak.

diabetes organizations and medical associations (20, 21). However, there is no evidence to assume that glucose peak coincides with 2-h glucose level after meal. We have attempted to give insight into the timing and size of post-meal glucose peaks occurring in the everyday life of type 2 diabetic patients, and into the respective role of glucose peak and 2-h glucose level on a consolidated surrogate marker of atherosclerosis such as carotid intima-media thickness (CIMT) (22).

Patients and Methods

Patients

The rationale and preliminary observational data of the ongoing Campanian post-prandial hyperglycemia group study have been published (23). Consecutive patients with type 2 diabetes were recruited among outpatients regularly attending diabetes clinics located in the area of the Campania County, South Italy, from 2001–2005. Inclusion criteria for the initial selection of patients were: a diagnosis of type 2 diabetes for at least 6 months but less than 10 yr, age 35–70 yr, body mass index (BMI) of 24 kg/m^2 or higher, HbA_{1c} of 6.5% or higher, and treatment with diet or oral drugs. Criteria for exclusion were: need for insulin use; concomitant chronic diseases, including kidney, liver, and cardiovascular diseases; recent acute illness; or change in diet, treatment, or lifestyle within the 3 months before the initial assessment.

After the initial screening visit, with verification of inclusion and exclusion criteria, all subjects were given the same model of glucose meter (One Touch and One Touch Ultra; Lifescan, Milan, Italy) and were instructed to familiarize themselves with glucose self-assessment with such a device for a period of 1–2 wk. They were then asked to measure home blood glucose on 3 nonconsecutive days during a period of 1 month. In particular, they assessed blood glucose just before and every 30 min after the main meal of the day (whether lunch or dinner) for 2 h (five readings). They were also asked to measure fasting glucose level at least twice on 2 nonconsecutive days during the month. Patients were invited to follow their usual treatment and eat their usual diet during the month. In particular, all patients had been instructed on diet and on the glycemic index of foods by a dietician at each diabetes clinic at least 3 months before study. The diet was recommended to be followed every day of the study, including those during which patients self-assessed blood glucose. The recommended composition of the dietary regimen was the following: carbohydrates 50–60%, proteins 15–20%, total fat less than 30%, saturated fat less than 10%, and less than 300 mg cholesterol consumed per day. All patients were invited to the reference center (Department of Geriatrics and Metabolic Diseases at the Second University of Naples) for blood sampling, and assessment of CIMT.

A total of 990 patients agreed to participate in the study and provided at least one complete (five readings) home blood glucose assessment. The present report focuses on the 644 patients who provided three complete home blood glucose profiles and had had CIMT assessment. Subjects providing complete glucose profiles had similar preprandial and postprandial glucose levels, and glucose changes after meals compared with those who provided incomplete data. We focused on subjects with complete data to have all statistical analyses performed on the same sample of subjects. Informed consent was obtained from every participant (not paid volunteer), and the study was approved by the local ethics committee.

Clinical and laboratory assessment

Height and weight were measured to the nearest 0.5 cm and 100 g, respectively, with participants wearing lightweight clothing and no shoes. BMI was calculated as weight in kilograms divided by height (in meters) squared. Blood pressure was measured with a mercury manometer, on the right arm, after 5-min rest in the sitting position.

Laboratory assessment was centralized. Blood glucose and serum lipids were measured by enzymatic assays in the hospital's chemistry laboratory, HbA_{1c} by nephelometry, and serum insulin by RIA (Pharmacia, Milan, Italy). The interassay coefficient of variation was less than 6% for all measurements.

Carotid B-mode ultrasound

Briefly, carotid sonography was performed on a single ultrasound machine (Aloka S.p.A., Assago, Italy) with a 7.5-MHz sector scanner probe. Studies were performed in a standard fashion by a single specialist physician who was specifically trained to perform the prescribed study examination. All images were electronically stored. The measurement was made in the 1-cm segment proximal to the dilation of the carotid bulb and always in plaque-free segments. For each patient, three measurements on both sides were performed, on the anterior, lateral, and posterior projection of the far wall; the readings were then averaged. Paired CIMT measurements in the same arteries showed a high degree of reproducibility, with a mean difference in CIMT of 0.020 mm, and an intraclass correlation coefficient of 0.97 ($P < 0.001$).

Analysis of glucose data

All premeal and post-meal glucose values represent the average of the three home blood glucose readings. Fasting glucose is the mean of the two home blood glucose assessments. Incremental glucose peak (IGP) was defined as the maximal incremental increase in blood glucose obtained at any point after the meal. The subjects were divided into quintiles of glucose peak (IGP). The rationale was based on the fact that absolute 2-h glucose values correlate positively with both fasting and premeal glucose levels; however, absolute increase of glucose above baseline correlate negatively with premeal glucose values (19). So, IGP may represent a good indicator of the reality of glycemic spikes occurring after a meal. Other glucose parameters were fasting glucose, premeal glucose, 2-h glucose, and absolute glucose peak, which is the highest glycemic value recorded at any time after the meal. In all patients, a subanalysis of the glycemic profiles was done in patients treated with diet.

Statistical analysis

Data are presented as mean (SD) unless stated otherwise. Standard procedures were used to calculate means, SD values, and linear correlation coefficients. Log-transformed glucose concentrations over the three study periods were tested for normal distribution using the test statistic for the Kolmogorov-Smirnov Goodness of fit for continuous data. Multiple regression models were used to explore the influence of different variables on CIMT and to adjust for covariates (24). Comparisons between variables in the different groups of patients were made using one-way ANOVA, followed by Tukey *post hoc* testing. CIMT was assessed in tertiles of IGP and HbA_{1c}, and the difference in CIMT in these tertiles was evaluated in trend. ANOVA for repeated measures was used to assess the reproducibility of glucose curves on different days. Changes in glucose, HbA_{1c}, lipids over time were evaluated using either a paired *t* test or Wilcoxon signed-rank test, as appropriate. $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS software (version 10.05; SPSS, Inc., Chicago, IL).

Results

Study subjects providing complete glucose profiles had similar demographic and clinical features compared with subjects not providing complete glucose profiles (data not shown). The main clinical and laboratory data are included in Table 1. The level of HbA_{1c} progressively increased across quintiles of IGP, as did triglycerides. Moreover, there was a progressive increase of CIMT from groups 1–5 (P for trend = 0.01 adjusted for age, lipid parameters, and HbA_{1c}). Adjustment for age and gender only did

TABLE 1. Clinical and laboratory data of study subjects

	Quintiles of IGP						
	1	2	3	4	5	Entire group	*P* value
IGP (mg/dl)	0–40	41–70	71–100	101–129	>130		
n	129	129	129	129	128	644	
No. of men/women	69/60	68/61	68/62	70/59	69/58	344/300	
Age (yr)	57.3 (7.0)	57.7 (6.9)	56.9 (7.0)	57.0 (6.7)	57.0 (7.2)	57.1 (7.8)	0.34
BMI (kg/m^2)	30.0 (5.0)	29.6 (5.1)	30.4 (5.0)	29.5 (4.8)	29.8 (5.0)	29.8 (4.9)	0.42
Glucose (mg/dl)							
Incremental peak	29 (12)	55 (16)	88 (15)	111 (18)	164 (17)	89 (56)	<0.001
Fasting	142 (40)	144 (51)	146 (46)	158 (53)	160 (59)	148 (35)	0.035
Premeal	147 (42)	140 (40)	140 (39)	136 (30)	129 (32)	137 (29)	0.028
2-h	160 (40)	164 (44)	175 (46)	282 (59)	212 (60)	177 (53)	<0.001
Absolute peak	179 (35)	189 (40)	209 (41)	235 (51)	295 (61)	220 (61)	<0.001
HbA_{1c} (%)	6.7 (0.8)	7.0 (0.9)	7.6 (1.2)	8.1 (1.2)	9.0 (1.3)	7.6 (1.3)	0.01
Fasting insulin (μU/ml)	13 (5)	14 (6)	14 (7)	12 (5)	13 (5)	13 (6)	0.19
Blood pressure (mm Hg)							
Systolic	142 (14)	140 (12)	141 (12)	140 (14)	142 (13)	141 (15)	0.23
Diastolic	84 (8)	83 (8)	82 (9)	83 (7)	83 (8)	83 (9)	0.26
Total cholesterol (mg/dl)	205 (35)	209 (37)	212 (33)	201 (29)	209 (31)	208 (34)	0.07
Triglycerides (mg/dl)	145 (59)	156 (57)	160 (51)	159 (60)	164 (62)	155 (53)	0.017
HDL cholesterol (mg/dl)	44 (9)	44 (10)	43 (9)	44 (10)	42 (9)	43 (10)	0.81
CIMT (mm)	0.82 (0.2)	0.84 (0.2)	0.86 (0.2)	0.92 (0.2)	0.94 (0.2)	0.88 (0.2)	0.01
Diabetes treatment (n)							
Diet	114	90	90	3	0	297	
Sulfonylurea alone	5	10	10	25	34	84	
Metformin alone	10	20	10	20	23	83	
Combined	0	9	19	81	71	180	
Other treatments (n)							
Lipid-lowering drugs	13	24	35	42	42	156	
Antihypertensive drugs	15	34	39	45	45	178	

Data are expressed as mean (SD) unless otherwise specified. To convert total and HDL cholesterol to mmol/liter, multiply by 0.0259. To convert triglycerides to mmol/liter, multiply by 0.0113. To convert glucose to mmol/liter, multiply by 0.0555.

not change the significance ($P = 0.01$). There was a similar trend in the relation between IGP and CIMT between sexes.

Relationships between CIMT and markers of glycemic control

When CIMT was tested for simple linear correlations against markers of glucose control, the strongest correlation was found with IGP (r = 0.40; $P = 0.006$). CIMT values in tertiles of IGP and HbA_{1c} are shown in Fig. 1. IGPs were associated with a significant increase in trend for CIMT in tertiles of HbA_{1c}.

A statistically significant correlation was also observed with absolute glucose peak (r = 0.35; $P = 0.01$), 2-h glucose (r = 0.24; $P = 0.02$), and HbA_{1c} (r = 0.21; $P = 0.03$). In contrast, CIMT did not correlate with fasting insulin (r = 0.15; $P = 0.08$), fasting glucose (r = 0.14; $P = 0.09$), total cholesterol (r = −0.02; $P = 0.82$), high-density lipoprotein (HDL)-cholesterol (r = −0.03; $P = 0.67$), and triglycerides (r = 0.14; $P = 0.08$). Age demonstrated a strong relation with CIMT (r = 0.38; $P = 0.001$).

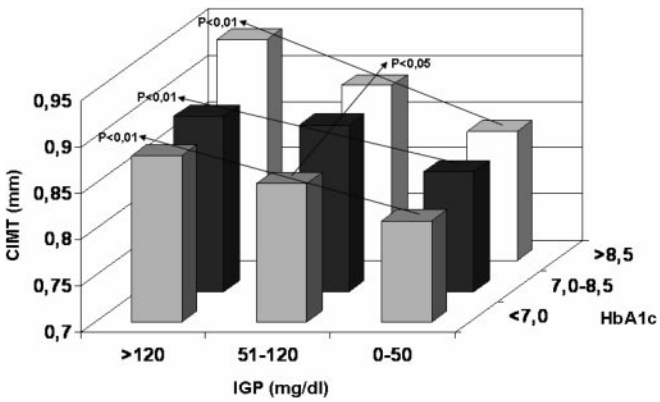

FIG. 1. CIMT (mm) in tertiles of IGP and HbA_{1c}.

Multiple linear regression analyses were performed to assess the independent effects of markers of diabetic control on CIMT. These markers included IGP, 2-h glucose, fasting insulin, and HbA_{1c}. Because correlations were observed between IGP and 2-h glucose (r = 0.55; $P < 0.001$) in the univariate analysis, two independent models were tested, one including IGP and one including the 2-h glucose value. The adjusted R^2 of model 1 (variables included HbA_{1c}, IGP, fasting insulin) was 0.26 ($P = 0.01$), whereas that of model 2 (variables included HbA_{1c}, 2-h glucose, fasting insulin) was 0.14 ($P = 0.03$). Apart from age, nonglycemic variables failed to enter the model when the stepwise regression analysis was applied to both glycemic and nonglycemic parameters.

Relationships among markers of glycemic control

High correlations were found between pre- and 2-h glucose levels, with r values around 0.50–0.60. Accordingly, when subjects were grouped according to mean preprandial glucose, we found that mean postprandial glucose increased across groups. However, IGP after a meal negatively correlated with prepran-

dial glucose levels, with r values in the range of 0.20–0.40 (Table 1). All these negative correlations were significant ($P = 0.01$). There was a strong correlation between IGP and absolute glucose peak ($r = 0.81$; $P < 0.001$). In the whole sample, both fasting ($r = 0.35$; $P = 0.01$) and 2-h ($r = 0.38$; $P = 0.01$) glucose levels, and absolute glucose peak ($r = 0.41$; $P < 0.001$) were significantly correlated to HbA_{1c}.

Timing and reproducibility of IGP

Figure 2 shows the home blood glucose profiles obtained on 3 different days. Blood glucose increase after meal was not different between days, with a high reproducibility for all values, including glucose peaks. The *P* values for the ANOVA for repeated measures were all above 0.1 (not significant). Moreover, IGP tended to occur at the same time. Ninety-five percent of the entire diabetic population studied (611 patients) had IGP occurring within 1 h from the start of the meal (257 at 30 min and 354 at 60 min).

Relationship between IGP and therapy for diabetes

Patients were classified into two groups according to whether they received drug treatment (n = 343) or diet alone (m = 301). Patients on drug treatment were more likely to have greater IGP levels as also indicated by a progressive shift of patient's number from quintiles 1–5: quintile 1, 114 patients on diet and 15 patients on drugs; and quintile 5, zero patients on diet and 128 patients on drug ($P = 0.01$). However, the timing of IGP was not different between the two groups (diet of drug), occurring for the most (94 and 95%, respectively) within 60 min after starting the meal.

Discussion

The results of the present study show that in patients with type 2 diabetes, IGP was correlated with CIMT more than markers of chronic hyperglycemia, including HbA_{1c} and fasting glucose concentration, as well as markers currently used to define postprandial hyperglycemia, such as 2-h blood glucose concentration. Moreover, post-meal glucose peak is reproducible in the same patient, and occurs within 1 h after start of meal. Together, these findings suggest that IGP describes at best the cardiovascular risk associated with acute glucose swings and occurs commonly in the everyday life of the diabetic patient. The vast majority of patients (94%) recorded blood glucose exceeding the American Diabetes Association and World Health Organization and thresholds for unacceptable postprandial hyperglycemia (≥160 mg/dl, 8.89 mmol/liter) (25) at any time after the meal. About 33% of patients studied had IGP decreasing in the range of 0–50 mg/dl; this may be due to an awareness of being in the study, influencing actual carbohydrate intake, or additional variables such as concomitant medications other than those asked for.

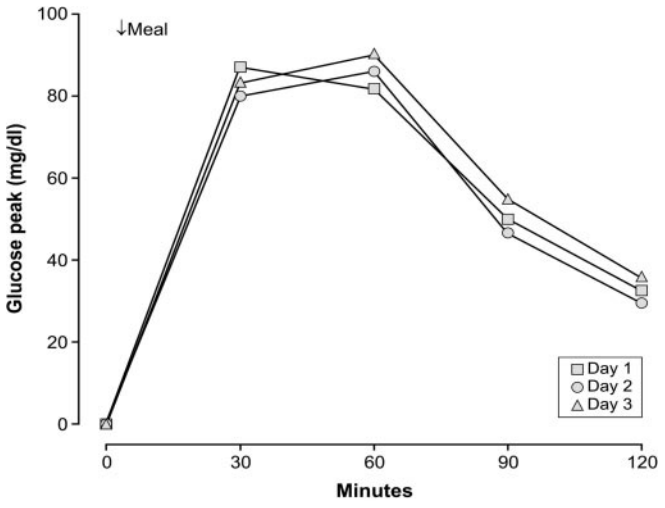

FIG. 2. Incremental glucose values after meal recorded at home on 3 different days in 644 diabetic patients. SD values are: 30 min (45, 48, and 44 mg/dl on d 1, 2, and 3, respectively); 60 min (47, 51, and 49 mg/dl); 90 min (26, 24, and 24 mg/dl); and 120 min (18, 19, and 20 mg/dl).

A stronger correlation between post-challenge hyperglycemic spikes compared with 2-h post-challenge hyperglycemia and CIMT has already been reported (26); however, to our knowledge, this is the first demonstration that IGP assessed at home in a free living condition is the best predictor of CIMT among all glycemic parameters usually used to identify hyperglycemia, both chronic and postprandial hyperglycemia (19, 26). Other risk factors of atherosclerosis such as hypertension, regular smoking, hyperlipidemia, and obesity (22, 27, 28) have also been described as being associated with CIMT. However, we found no correlation between CIMT and such parameters as BMI, blood pressure, and serum lipid concentrations.

The metabolic abnormalities that characterize the development of type 2 diabetes are first demonstrated before clinical diabetes by elevations in postprandial glucose, due to the loss of first-phase insulin secretion, decreased insulin sensitivity in peripheral tissues, and reduced suppression of hepatic glucose output after meals due to insulin deficiency (29, 30). Monnier *et al.* (31) demonstrated that the gradual loss in daytime postprandial glycemic control precedes a stepwise deterioration in nocturnal fasting periods with worsening diabetes. In particular, nocturnal fasting glycemic control remains essentially unchanged as long as the HbA_{1c} level is less than 8%, whereas postprandial glucose control is subject to much earlier deterioration, occurring as soon as HbA_{1c} levels increase above 6.5%. Thus, a patient who had relatively normal fasting glucose values will exhibit abnormal elevations of glucose levels after meals. These findings are supported by interventional trials showing that patients who achieved fasting plasma glucose below the targets still exhibited A1C levels more than 7% (32).

Post-meal glucose levels seldom increase above 140 mg/dl (7.77 mmol/liter) in subjects with normal glucose tolerance and then return to basal levels 2–3 h after food ingestion (33, 34). However, the current consensus of the American Diabetes Association is that postprandial glucose should not necessarily be systematically monitored, and that postprandial glucose peaks should not necessarily be targeted and corrected (34), although, if monitored, the recommended goal for postprandial glucose is less than 10.0 mmol/liter (180 mg/dl) (35). Bonora *et al.* (19) obtained daily glucose profiles from 3284 type 2 diabetic patients and recorded a postprandial glucose value more than 160

mg/dl (8.89 mmol/liter) at least once in 84% of patients. These figures are consistent with data on post-oral glucose tolerance test hyperglycemia collected in diabetic patients from the National Health and Nutrition Examination Survey (18).

Large epidemiological studies have shown a strong association between post-meal and post-challenge glycemia and cardiovascular risk and outcomes in individuals with normal glucose tolerance, impaired glucose tolerance, or diabetes (9, 10, 36, 37). Furthermore, a large and growing body of evidence shows a causal relationship between post-meal hyperglycemia and oxidative stress, carotid atherosclerosis and endothelial dysfunction, all of which are known markers of cardiovascular disease (12–15, 38, 39). Monnier *et al.* (40) assessed 24-h urinary excretion rates of free 8-iso prostaglandin $F_{2\alpha}$ as a reliable marker of oxidative stress and used continuous glucose monitoring to assess glucose fluctuations. Results showed that glucose fluctuations during postprandial periods exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia in type 2 diabetic patients compared with nondiabetic subjects.

Interventional trials also suggest a link between postprandial hyperglycemia and cardiovascular risk. The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus trial has shown that treatment of subjects with impaired glucose tolerance with the α-glucosidase inhibitor acarbose, a compound that specifically reduces postprandial hyperglycemia, is associated with a 36% reduction in the risk of progression to diabetes (41), 34% risk reduction in the development of new cases of hypertension, 49% reduction in the risk of cardiovascular events (42), and a slower progression of CIMT (43). We have previously reported (23) a significant positive effect of post-meal glucose control on CIMT in 175 drug naive type 2 diabetic patients who were treated with repaglinide, a rapid-acting secretagogue that targets post-meal glucose. After 12 months, CIMT regression, defined as a decrease of more than 0.020 mm, was observed in 52% of diabetics receiving repaglinide and in 18% of those receiving glyburide.

In conclusion, this study demonstrates that an IGP value higher than 50 mg/dl (2.78 mmol/liter) is a frequent event in the everyday life of type 2 diabetes, occurs in about two thirds of patients, and correlates with CIMT. Moreover, 2-h postprandial glucose should not be considered as equivalent to post-meal glucose peak. For practical purposes, a 1-h glucose reading after meal represents a good estimate of absolute glucose peak ($r = 0.84$; $P < 0.001$), but future research on this topic is needed. Weaknesses of the present study are its observational nature, and results limited to people with type 2 diabetes and poor glycemic control. Strengths of the study are home assessment of glucose values instead of the artificial context of an oral glucose tolerance test, repetition of glucose profile within 1 month, centralization of analyses and CIMT, and the quite large number of patients investigated. Attention to post-meal glucose peak hopefully will provide an additional benefit to efforts to normalize HbA_{1c} and premeal glucose value.

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