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Predicting more accurately the overall glucose response to a lunch meal by using the postprandial glucose peak

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Abstract

Although the assessment of postprandial glycemia is clinically important, the most relevant time points with the smallest number of blood samples giving the highest predictive power have yet to be established. It has been suggested that a sample estimating the postprandial peak concentration would improve this predictive power compared to the usual recommended time points. In this study, we assessed the power of these time points to predict the glucose response to a meal mimicking everyday life. Subjects were 11 healthy young men (mean age, 22 ± 1 years; body mass index, 21.7 ± 1.8 kg/m^2). Plasma glucose, insulin, and nonesterified fatty acids were measured by continuous collection of blood in tubes filled every 5 minutes for 240 minutes after a 2-item lunch meal consumed ad libitum on the first test day, and in the same amount 1 week later. The most relevant time point for the plasma glucose peak level was found at 45 minutes (mean interval, 47 ± 3 minutes) and was not dependent on the energy intake at lunch. Its coefficient of variation was low (7.0% ± 1.5%). The best predictive equation for the whole postmeal glucose area under the curve (AUC) was found at 120 minutes and involved glucose, insulin, and nonesterified fatty acids (r^2 = 0.89; $P < 10^{-7}$). The 120-minute postmeal glucose profile constructed with the 0-, 45-, 90-, and 120-minute time points overlapped more accurately with the actual profile than did the time points normally used in the glucose tolerance test, and slightly improved the correlation between the calculated and the actual plasma glucose area under the curve (r = 0.96; $P < 10^{-7}$). In conclusion, in healthy, young, lean male subjects, a blood sample collected 45 minutes after a spontaneous lunch meal estimates the postprandial plasma glucose peak and suggests that including the peak level along with 90- and 120-minute time points may improve the predictive power of the plasma glucose profile after a meal.

1. Introduction

It has been suggested that a standardized, mixed test meal would be more efficient than an oral glucose tolerance test (OGTT) for assessing impaired glucose tolerance (IGT) or diabetes [1-5]. A postmeal glucose tolerance test may avoid the low acceptability of the glucose load and improve reproducibility. More recently, postprandial hyperglycemia has been considered as a possible independent cardiovascular risk factor [6-11] and among all blood glucose levels tested over the day, only blood glucose after lunch predicted cardiovascular events [12], providing strong support for this hypothesis. This led some authors [13] to conclude that "early interventional data suggest that therapy targeted at postprandial glucose can have a favorable impact on cardiovascular events." Others [14] proposed trying to restrict glucose to less than 180 or less than 140 mg/dL over postbreakfast or postlunch periods. However, the time points most predictive of the overall glucose response to the meal are unknown.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [15] and the World Health Organization [16] have restricted the diagnosis of diabetes mellitus to the value of the blood glucose concentration after an 8-hour fast or to a glucose measurement 120 minutes after a 75-g glucose load dissolved in water. The other time points recommended for measuring plasma glucose to diagnose diabetes or IGT are fasting level and 30, 60 [17], or 90 minutes [18] after either a glucose load (range, 50-100 g) or a standard test meal [19].

In our 10 years' experience analyzing postmeal blood glucose profiles using continuous blood collection, we

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found that the 120-minute time point measurement occurs during a phase of high variability. This is accounted for by the fact that in most healthy subjects, plasma glucose and insulin concentrations are biphasic after either a glucose load [20,21] or a lunch meal [22]. This variability could alter the relevance of this time point if a high glucose level corresponds to a second glucose peak profile in some but not all subjects. Moreover, the power of the different time points to predict the total glucose response to a meal has not been assessed, mainly because it needs a reference condition requiring frequent or even continuous blood collection. Last, because of the importance of a peak in pulsatile mechanisms, it seems important to test the predictive power of the time point most relevant to the postprandial glucose peak.

In the present study, blood was continuously withdrawn and collected in tubes changed every 5 minutes. We measured plasma glucose, insulin, and nonesterified fatty acid (NEFA) concentrations over 4 hours after a lunch meal, and measurements were taken twice with an interval of 1 week between the two. The time points most relevant to the peak level and the lowest coefficient of variation (CV) for predicting the overall glucose response were assessed. The best geometrical construction of the actual glucose response was tested with the time points usually recommended and with time points that we thought followed more accurately the actual blood glucose profile.

2. Materials and methods

2.1. Subjects

After approval of the protocol by the Ethics Committee in Human Research of Aulnay-sous-Bois, France, subjects were recruited through advertisements posted in the Xavier Bichat Medical School (Paris, France). Subjects were excluded if they were smokers; were trained athletes; took medication; reported a personal or family history of obesity, diabetes, or other metabolic disease; or reported a change in body weight of ±2 kg over the 3 years before the study. The experiment was completed by 11 lean and healthy men aged 22 ± 1 years (mean ± SEM). Body mass index for the group was 21.7 ± 1.8 kg/m^2. Fat-free mass and fat mass were assessed by using the subcutaneous skinfold thickness method and were estimated at 61.1 ± 6.1 and 9.0 ± 2.4 kg, respectively. Subjects gave written informed consent before the experiment and were financially compensated for completing the study.

2.2. Procedure

Subjects came to the laboratory on 2 occasions separated by an interval of 1 week. Subjects were asked to eat the same breakfast on the morning of the experimental days. This was checked with the investigator on the second session. They arrived at the laboratory at 12:15 PM. They were deprived of time cues by exposing them to artificial light and by removing all sources of visual and auditory time cues as previously described [23]. At 12:30 PM, an indwelling catheter was inserted into an antecubital vein and saline was infused for 30 minutes. Blood withdrawal started at 1:00 PM and was uninterrupted throughout the experiment. Lunch was served 30 minutes after the first blood sampling. On the first test day, subjects were told to eat as much or as little as they wanted, and meal duration was not fixed to encourage ad libitum intake. The same amount was served on the second test day, and subjects were required to eat all of it.

2.3. Test meal

Lunch meal consisted of a main dish, spaghetti "bolognaise" (5.2 kJ g^{-1}; 56% carbohydrate, 18% fat, 26% protein), and a dessert item, praline-flavored dessert cream (6.2 kJ g^{-1}; 57% carbohydrate, 30% fat, 13% protein).

2.4. Biochemical analyses

As described in detail elsewhere [23], a specially designed double-lumen catheter (MTB, Amstetten, Germany) was inserted into the antecubital vein and blood was withdrawn continuously throughout the session. Sample tubes were filled every 5 minutes and were immediately centrifuged at 4°C. Plasma was frozen to −30°C for subsequent assays. Plasma assays for glucose, insulin, and NEFA followed standard procedures. Insulin was determined by radioimmunoassay using the SB-INSI-5 kit (CEA, Gif-sur-Yvette, France; 7% accuracy) with a lower level of sensitivity of 2 μU mL^{-1}. Glucose was measured by the glucose oxidase enzymatic method in a Yellow Spring glucose analyzer (Bioblock, Strasbourg, France; 1% accuracy). NEFA concentrations were measured by the colorimetric enzymatic method using a C Wako kit (Oxoïd, Dardilly, France; 5% accuracy).

2.5. Statistical analyses

Peaks were determined, in each subject and in each test, as time points preceded and followed by at least 2 increasing and decreasing points. To select the most relevant time point for the first postprandial glucose peak, we first noted the time point where this peak occurred most often, and then we calculated the mean time interval to this peak. To be selected, the time point had to be the closest to the mean interval and the one displaying the most peaks. A glucose area under the curve (AUC) (glucose$_{AUC}$) was determined by using the trapezoidal method without subtraction of a basal AUC because the total was more important than the incremental area [24]. The CV of each time point and of glucose$_{AUC}$ was calculated for each subject according to the equation CV = 100 × SD/M, where SD is the standard deviation of the repeated tests calculated for each subject and M the mean value of the 2 tests observed for each subject. Then the mean CV was calculated for the group as the mean of all individual CVs. The lowest CV was calculated by using the same procedure

as for the peak level, ie, the time point where this lowest CV occurred most often and the mean time interval to this lowest CV value. Then CVs at different time points were subjected to univariate analysis of variance (ANOVA) for repeated measures using SYSTAT software (version 10.2, SPSS, Chicago, IL). When significant, differences between means were compared by the Scheffe method. Correlations between plasma glucose samples and $glucose_{AUC}$ were conducted according to Pearson. We also wanted to find out if the size of the meal altered the reproducibility of the different time points and if one of the items contributed more than the others did to this effect. Thus, a correlation between the amount of each item eaten and the mean CV of each selected time point was conducted. To determine which time points were the best to predict the actual glucose response to the meal, multivariate linear regression analyses were conducted, based on a backward stepping procedure. The significance for including or rejecting a predictor was set at .05. The relation between calculated AUC and the actual AUC calculated from all the blood glucose concentrations at 5-minute intervals was then assessed by Pearson correlation. Lastly, the 120-minute $glucose_{AUC}$ was modeled using 3 methods: a 3- and a 4-time-point (0, 60, and 120 minutes and 0, 30, 60, and 120 minutes, respectively) method [24] and a 4-time-point method based on the observation of the actual profile and involving the peak value. The areas obtained were first compared graphically to the actual one and Pearson correlations were calculated between each of these AUCs and the actual $glucose_{AUC}$. A P value less than .05 was accepted as significant.

3. Results

3.1. Food intake

Mean energy intake at lunch was 3425 ± 196 kJ for the group (range, 2493-4500 kJ) with a mean of 116 ± 7 g carbohydrates (range, 84-152 g), 25 ± 1 g fat (range, 18-33 g) and 33 ± 2 g protein (range, 25-43 g). Time taken to eat was 17 ± 4 minutes.

3.2. Postprandial plasma pattern

The most frequent interval to the glucose peak was 45 minutes (8 of 22). For the 22 tests, the mean interval between the beginning of the meal and the glucose peak was 47 ± 3 minutes with a within-subject CV of 8.6 ± 2.2%. The 45-minute time point (mean, 7.0 ± 0.2 mmol L^{-1}; CV, 7.0% ± 1.5%) was therefore chosen to represent the mean postprandial glucose peak. The lowest CV was more difficult to determine. Analyses showed that there were 2 periods of low CV of plasma glucose, the first during the 10 minutes preceding the peak and the second between 180 and 220 minutes (Fig. 1A). The lowest CV was observed at 35 minutes (4.7% ± 1.0%) for the first and at 205 minutes (5.1% ± 1.3%) for the second. Interestingly, the CVs of plasma glucose at 90 (14.2% ± 2.5%) and 120 minutes (11.9% ± 3.0%) were both higher than at 35, 45, and 205 minutes (all $P < .05$). Mean postprandial plasma concentration and CV of insulin and NEFA are shown in Fig. 1B and C, respectively. As expected, the insulin profile was close to the glucose profile, whereas the postprandial NEFA response showed the usual steep decline during the 60 minutes after the onset of the lunch meal, followed by low concentrations over the further 180 minutes. Mean CV for insulin (27.2% ± 5.9%) and for NEFA (24.2% ± 4.9%) were higher than for glucose (8.2% ± 1.7%) (both $P < .001$).

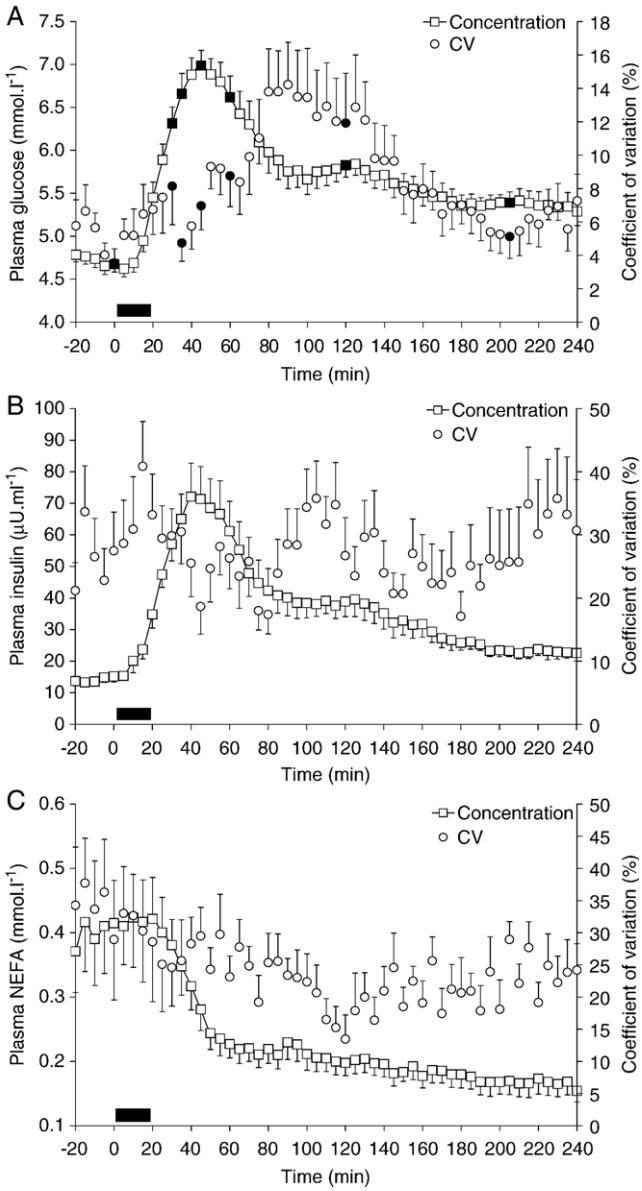

Fig. 1. Mean (±SEM) postprandial plasma concentrations (squares) and CVs (circles) of glucose (A), insulin (B), and NEFAs (C). Time points selected for correlations and predictive equations (see text) are indicated by closed symbols. Lunch meal (black rectangle) was ad libitum for each subject on the first test day, but the same in both tests.

Table 1
Coefficients of correlation (r) between plasma glucose at the different selected time points and mean plasma glucose$_{AUC}$ from 0 to 240 minutes after lunch

Time point (min)	Day	r	P
Basal	1	0.31	NS
	2	0.04	NS
30	1	0.23	NS
	2	0.34	NS
35	1	0.21	NS
	2	0.42	NS
45	1	0.19	NS
	2	0.89	<.005
60	1	0.60	<.05
	2	0.93	<.0001
120	1	0.80	<.005
	2	0.99	<.0001
205	1	0.12	NS
	2	0.78	<.005

NS indicates not significant.

A biphasic pattern was found for both tests in 9 of the 11 subjects, in only 1 test in 1 subject, and in none of the tests in another subject. A third peak was observed in both tests for 4 subjects, in 1 test for 4 subjects, and in none of the tests for 3 subjects.

Mean plasma glucose$_{AUC}$ was similar throughout the 2 test days (1468 ± 30 and 1467 ± 45 mmol L^{-1} min^{-1} on the first and second days, respectively) with a within-subject CV of 8.1% ± 0.7%, but these AUCs were only moderately correlated (r = 0.60; P < .05).

3.3. Correlations and predictive equations

There were no correlations between energy intake at lunch and (1) the level of plasma glucose at each of the selected time points, (2) the interval to the individual peaks, and (3) the glucose$_{AUC}$. Energy intake at lunch was negatively correlated with glucose CV at 45 minutes (r = −0.73, P = .01), but not at the other time points. This correlation was due to the dessert item (r = −0.78, P = .004) and not to the main dish (r = −0.26; not significant).

As shown in Table 1, among the selected time points, the 60- and 120-minute time points were the only ones correlated on both days with the total glucose$_{AUC}$. The 120-minute time point showed the highest correlation

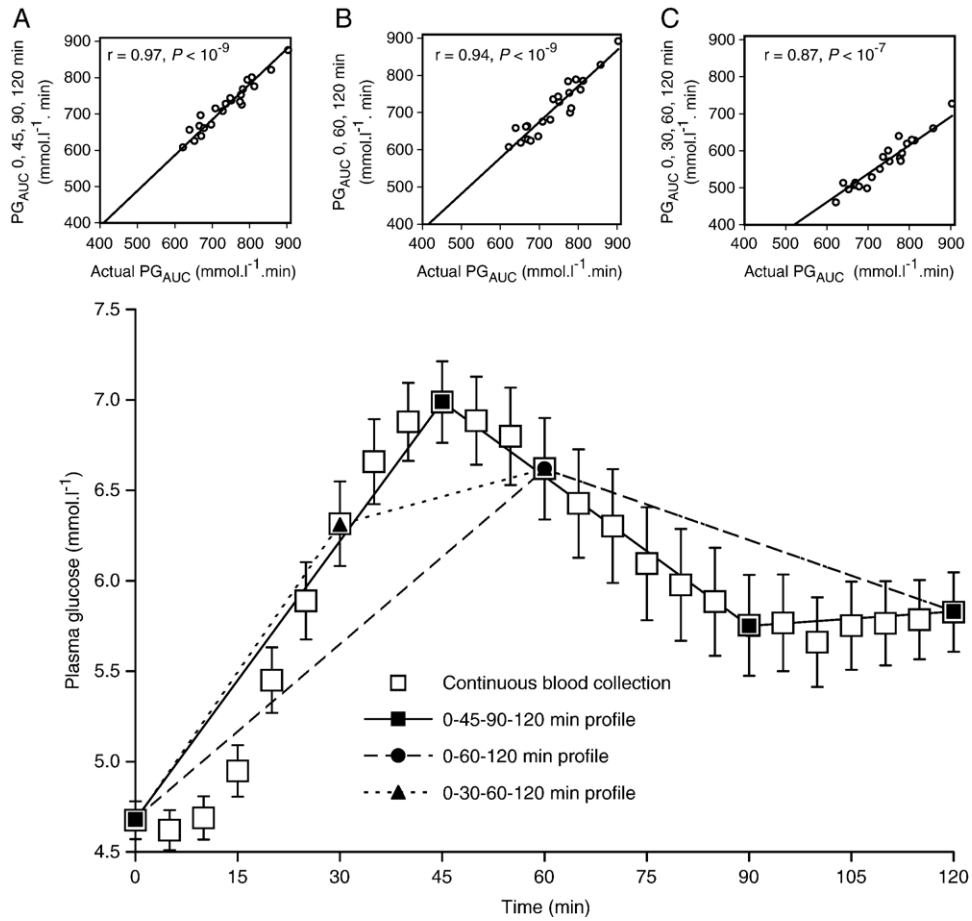

Fig. 2. Mean (±SEM) 120-minute postprandial plasma glucose concentrations from continuous blood collection (white squares) and profiles constructed with 0-, 45-, 90-, and 120-minute (black squares, plain line), 0-, 60-, and 120-minute (black circles, long dotted line), and 0-, 30-, 60-, and 120-minute (black triangles, short dotted line). Inset: correlations between plasma glucose$_{AUC}$ (PG_{AUC}) constructed with the 0-, 45-, 90-, and 120-minute (A), 0-, 60-, and 120-minute (B), and 0-, 30-, 60-, and 120-minute (C) time points. Regression equations: Actual PG_{AUC} = 1.05 × AUCc − 20 (A), Actual PG_{AUC} = 0.9 × AUCc + 86 (B), and Actual PG_{AUC} = 0.64 × AUCc + 265 (C), where AUCc is calculated area under the curve.

coefficients on each day. Consistently, the best fitting equation to predict mean $glucose_{AUC}$ was found for the 120-minute measurement and involved glucose, insulin, and NEFA as predictive factors. The regression equation was $G_{AUC} = (151.7 \times G) - (1.01 \times I) - (374.7 \times NEFA) + 697.4$ ($r^2 = 0.89$, $P = 10^{-7}$), where G_{AUC} is the plasma $glucose_{AUC}$, and G, I, and NEFA are plasma glucose (in millimoles per liter), insulin (in microunits per milliliter), and NEFA (in millimoles per liter) concentrations at 120 minutes, respectively. Using only glucose concentration, the best regression model for $glucose_{AUC}$ was also found at 120 minutes. The regression equation was $G_{AUC} = 642.8 + 141.5 \times G$, where G is the glucose level at 120 minutes ($r^2 = 0.83$).

Looking at the actual glucose profile obtained with the continuous blood collection procedure, we chose to test the validity of the 0-, 45-, 90-, and 120-minute time points to best reconstruct the glucose profile over the 120 minutes after lunch. As illustrated in Fig. 2, the profile constructed with these time points overlapped more accurately with the actual glucose profile than did the profiles constructed with the 0-, 60-, and 120-minute and the 0-, 30-, 60-, and 120-minute time points. Moreover, the $glucose_{AUC}$ constructed with the 0-, 45-, 90-, and 120-minute time points was strongly correlated (see Fig. 2A-C) with the actual $glucose_{AUC}$ in the first and second test sessions ($r = 0.97$ and $r = 0.98$, respectively; $P < 10^{-7}$), these correlations being slightly less reproducible for the $glucose_{AUC}$ calculated with the 3 ($r = 0.89$; $P < .001$ and $r = 0.97$; $P < 10^{-7}$, respectively) and 4 time points ($r = 0.92$; $P < 10^{-5}$ and $r = 0.97$; $P < 10^{-7}$, respectively).

4. Discussion

There is increasing evidence for the need to evaluate the postmeal glucose profile for prevention of glucose-induced heath risks, especially cardiovascular complications [6-12]. Analysis of the physiologic glucose response to a normal mixed meal and the detection of the most relevant moment for collecting blood are important. The first objective of the present study was to determine a time point measurement relevant to the postprandial glucose peak in healthy young subjects eating ad libitum a mixed meal and in the same amount 1 week later. Consistent with previous results [1], 45 minutes was found to be the interval that best represented this peak. Although energy intake varied between subjects (from about 2500 to 4500 kJ), the peak glucose concentration lay in a narrow range with a mean value at 7.4 ± 0.1 mmol L^{-1}. In the study of Heim et al [2] using 2215 and 3250 kJ mixed meals containing 100 and 150 g carbohydrates, respectively, and with continuous blood sampling, the peak level was found at 35 ± 3 minutes and reached 6.7 ± 0.2 mmol L^{-1} with no difference between the 2 test meals or compared with the 100-g glucose load. Other authors [22] supplying volunteers with 40% of their daily energy requirements at lunch reported a first postprandial peak 60 minutes after the start of the meal with a mean level at 7.3 ± 0.7 mmol L^{-1}. The differences in the interval to the first peak between these studies and ours could be due to the use of breakfast instead of lunch in the first [2] and collection of blood every 15 minutes instead of 5 minutes in the second [22].

In common with authors using a continuous [25] or prolonged measurement of blood glucose [22], we observed a second peak in most cases. Among our 11 subjects, 9 displayed this peak on both tests about 135 minutes after lunch. The 2 subjects not exhibiting the biphasic pattern in the tests had similar pre- and postmeal glucose levels to the rest of the group. Interestingly, the biphasic pattern has been proposed for the screening of glucose tolerance in epidemiologic studies [21]. We noted a third peak about 215 minutes after lunch in both tests in 4 of our subjects.

The second objective of this study was to determine which time point displayed the lowest CV, this being an important issue for the validity of the measurement. Two time windows were found, one early after lunch with a mean delay of 35 minutes, one later with a mean delay of 205 minutes. These time points had not only the lowest CV, but also less than half the CV of the 120-minute time point. Our CV at 120 minutes (11.9% ± 3.0%) was close to those found by other authors. Wolever et al [5] reported a 9.2% ± 1.9% CV and a 13.1% ± 2.1% CV 120 minutes after oral glucose loads and a standardized test meal, respectively. In agreement with a later study by Wolever [26], we noted that the CV of glucose was much higher during the second than during the first postprandial hour, probably stemming from the within-subject variation of the second glucose peak. This CV decreased slowly to the preprandial level over the third and fourth hours. Interestingly, energy intake at lunch had no influence on these glucose CVs except at 45 minutes where the correlation was negative and exclusively due to the dessert item. Thus, the within-subject difference of the glucose peak level between the 2 sessions was even more elevated that the second item of this two-item meal was high in energy. The higher glycemic index of the praline-flavored dessert cream may in part account for this effect. If the peak level is to be used as a criterion, the meal structure will therefore need to be taken into account.

The first basis for selecting a time point is the observation that the glucose concentration is predictive of the overall postprandial glucose response, which is best evaluated by using the AUC method. Measurement of glucose levels 120 minutes after an oral glucose load is currently exploited for the diagnosis of diabetes or IGT [15]. Our results show that this time point was the most consistently correlated and the best for predicting total postprandial $glucose_{AUC}$. However, the correlation coefficients between glucose concentrations at each time point and $glucose_{AUC}$ were lower on the first test than on the second test day. One explanation could be a “first meal effect” [27] attributed to stress-induced epinephrine giving rise to higher glucose concentrations in response to the meal. In our study, the $glucose_{AUC}$ was not higher on the

first than on the second test day. However, this weaker correlation on the first session should be taken into account and could reduce the clinical value of the postmeal glucose test.

The 45- and 205-minute time points did not improve the estimation of the actual $glucose_{AUC}$. On the contrary, their correlation was weak or nonsignificant (eg, on day 1), whereas the 120-minute time point showed a high and consistent predictive power. Interestingly, this power was slightly enhanced by inclusion of the insulin and NEFA concentrations in the model, arguing for a role of NEFA in the glucose response to a meal, probably via its effect on insulin secretion [28]. However, in our models, NEFA concentrations did not provide a more accurate estimation of $glucose_{AUC}$ when insulin was excluded from the equation.

Although the official statement for diagnosing IGT is based on the 120-minute plasma glucose level, the plasma $glucose_{AUC}$ is often evaluated by using the 4 OGTT time points (0, 30, 60, and 120 minutes) [29], and a 3-time-point OGTT (0, 60, and 120 minutes) has even been described as the method of choice [30]. Different trials of indexes for glucose tolerance usually involve the 0-, 30-, 60-, and 120-minute time points [31]. We found that in our healthy subjects, these 4- and 3-time-point profiles did not overlap as well as the 0-, 45-, 90-, and 120-minute profile did with the actual profile. These 4 time points were chosen after a careful visual analysis of all the profiles. Interestingly, the difference between the predictive power of these different constructions could not be identified from the correlations alone, as the underestimation of the 0- to 60-minute interval was compensated for by the overestimation of the 60- to 120-minute interval. However, it is more satisfying to have time points that accurately follow the actual profile as is the case with the 0-, 45-, 90-, and 120-minute samples. Interestingly, including the 90-minute time point in the equation of insulin sensitivity has been shown to improve the predictive power of the OGTT [18]. Consistently, using frequent blood sampling (0, 8, 15, 22, 30, 45, 60, 90, 105, and 120 minutes), other authors [32] concluded that the 3-sample method (0, 30, and 60 minutes) led to an overestimation of the insulin sensitivity. Because our subjects had normal glucose tolerance, a similar protocol in subjects with abnormal carbohydrate tolerance and diabetes could be useful to validate this time point selection in target populations. However, it should be noted that no procedure of this kind had been conducted before the recommendations of the various proposed time points.

Energy intake has been found to have little influence on the glucose response to meals eaten in everyday life conditions even in diabetic patients [33]. Our results obtained in nondiabetic and nonobese lean subjects are consistent with a weak relation between energy intake at lunch and subsequent glucose levels (time points or AUC). Nevertheless, the type of food, especially the glycemic index of the carbohydrate in the meal, is a potent determinant of the glucose response [34]. A rather high carbohydrate meal was chosen for this first explorative study. Moreover, this test meal (based on carbohydrate derived from spaghetti) can be considered to have a low glycemic index. Thus, our results can be considered relevant to the intraindividual variability after a low-fat and low-glycemic-index meal, as usually recommended in diabetes, but should not be extrapolated to meals of higher glycemic index that will require evaluation.

In conclusion, our results obtained in young, lean, and nondiabetic male subjects argue for substituting a 45-minute time point for the 30- and 60-minute time points if several samples have to be collected to evaluate the glucose response to lunch. They appeared to be the most relevant to the post-meal plasma glucose peak level and improved the accuracy of the overall postprandial profile. However, for a single measurement, the 45-minute time point appears to be less accurate and less reproducible than the 120-minute time point to predict the overall glucose response to lunch meal. Further research including subjects with obesity and subjects with impaired tolerance to glucose or diabetes would be necessary to confirm these findings in nonhealthy populations.

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