Impact of Glucose Tolerance Status, Sex, and Body Size on Glucose Absorption Patterns During OGTTs

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OBJECTIVE—We studied whether patterns of glucose absorption during oral glucose tolerance tests (OGTTs) were abnormal in individuals with impaired glucose regulation and whether they were related to sex and body size (height and fat-free mass). We also examined how well differences in insulin sensitivity and β-cell function measured by gold-standard tests were reflected in the corresponding OGTT-derived estimates.

RESEARCH DESIGN AND METHODS—With validated methods, various aspects of glucose absorption were estimated from 12-point, 3-h, 75-g OGTTs in 66 individuals with normal glucose tolerance (NGT), isolated impaired fasting glucose (i-IFG), or isolated impaired glucose tolerance (i-IGT). Insulin sensitivity and β-cell function were measured with the euglycemic-hyperinsulinemic clamp and intravenous glucose tolerance tests, respectively. Surrogate markers of both conditions were calculated from OGTTs.

RESULTS—More rapid glucose absorption ($P \leq 0.036$) and reduced late glucose absorption ($P \leq 0.039$) were observed in the i-IFG group relative to NGT and i-IGT groups. Women with i-IGT had a lower early glucose absorption than did men with i-IGT ($P = 0.041$); however, this difference did not persist when differences in body size were taken into account ($P > 0.28$). Faster glucose absorption was related to higher fasting ($P = 0.001$) and lower 2-h ($P = 0.001$) glucose levels and to greater height and fat-free mass ($P < 0.001$). All OGTT-derived measures of insulin sensitivity, but only one of three measures of β-cell function, reflected the differences for these parameters between those with normal and impaired glucose regulation as measured by gold-standard tests.

CONCLUSIONS—Glucose absorption patterns during an OGTT are significantly related to plasma glucose levels and body size, which should be taken into account when estimating β-cell function from OGTTs in epidemiological studies.

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Individuals with the prediabetic conditions of impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT) have a higher risk of developing type 2 diabetes than do individuals with normal glucose tolerance (NGT) (1,2). Several studies have shown that men in general have higher fasting plasma glucose (FPG) levels and a higher prevalence of isolated IFG (i-IFG) than do women (3–6). In contrast, women often exhibit higher glucose levels after a standard 75-g oral glucose tolerance test (OGTT) and consequently have a higher prevalence of isolated IGT (i-IGT) (3,4,6) than do men. We and others have previously suggested that the difference in post-OGTT glucose concentration is a consequence of the relatively higher dose of glucose given to women compared with men when seen in relation to their body size (3,4,7). Specifically, it has been shown that there are no sex differences in post-OGTT 2-h plasma glucose (2hPG) levels after adjustment for body height (3,4,7). It has also been suggested, however, that the higher 2hPG levels in women may be attributed to differences in glucose absorption patterns between men and women (8). Healthy women with NGT seem to have lower glucose absorption from the gut during the first hour of an OGTT than do their male counterparts, whereas glucose absorption is higher in women than in men during the last hour of a 3-h OGTT (8). Whether such sex differences in glucose absorption patterns can be explained by differences in body size has not been previously determined.

Several factors influence blood glucose concentrations after a meal or an OGTT. In addition to gastric emptying and small intestine digestion and absorption, peripheral insulin sensitivity and the amount of insulin secreted in response to glucose and incretin hormones are major determinants of postprandial or post-OGTT glucose concentration (9–11). The relative contributions of these various factors remains uncertain and controversial (10). More than 20 years ago it was shown that the amount of glucose absorbed in response to varying glucose loads is diminished in individuals with type 2 diabetes (12). Furthermore, a recent study showed that pregnant women with gestational diabetes mellitus had markedly lower glucose absorption than pregnant women with NGT (13). The mechanisms underlying these associations are not well understood. Moreover, it is unclear whether defects in glucose absorption are already present in individuals with slightly elevated blood glucose levels, those with IFG or IGT.

Through the use of OGTTs, many methods for estimating β-cell function and insulin sensitivity have been suggested (14–16). These estimates reflect discrete aspects of β-cell function (first phase, second phase, static, dynamic) and more or less specific sites of insulin sensitivity (liver, periphery, whole body), but none of them take into account potential differences in glucose absorption patterns among the tested persons. In this

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study, we examined whether patterns of glucose absorption during OGTTs differed between individuals with normal and impaired glucose regulation and whether they were related to sex and body size. In addition, we examined how well the differences in insulin sensitivity and β-cell function between normal and impaired glucose regulation as estimated by gold-standard tests were reflected in the corresponding OGTT-derived estimates.

RESEARCH DESIGN AND METHODS

Study participants

A subset of study participants of white ethnicity were recruited from the Danish nonpharmacological intervention study Inter99. The Inter99 study aimed to examine the effect of a nonpharmacological intervention on the development of diabetes and cardiovascular morbidity and mortality (17). A total of 6,784 participants were examined with a standard 75-g OGTT at baseline (1999–2001). After 5 years of follow-up, all participants were invited to a clinical examination, including an OGTT, to determine glucose tolerance status. We subsequently invited a subset of 66 individuals who had progressed from NGT (FPG <6.1 and 2hPG <7.8 mmol/L) to i-IFG (n = 18, FPG ≥6.1 and 2hPG <7.8 mmol/L) or i-IGT (n = 28, FPG <6.1 and 2hPG ≥7.8 mmol/L) during the 5 years of follow-up, as well as a control group who had NGT both at the baseline and at the 5-year follow-up examination (n = 20). For each glucose tolerance group, we aimed for equal proportions of men and women; however, we were only able to recruit two women with i-IFG and thus could not study sex differences in that particular group. A group with combined IFG and IGT was not included, because the aim of the study was to examine the mechanisms responsible for isolated defects in fasting and 2-h glucose metabolisms. Further details about recruitment, classification, and study population have been published elsewhere (18,19). All study procedures took place at Steno Diabetes Center A/S, Gentofte, Denmark, in 2005–2007. All study participants gave written informed consent to participate, and the study was approved by the local ethics committee and conducted in accordance with the Helsinki declaration.

Examinations

Standard 75-g OGTTs were performed after an overnight fast. Samples were drawn at −10, 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, and 180 min for assessment of plasma glucose and serum insulin concentrations. On a separate day, the 66 participants underwent an examination of insulin sensitivity and β-cell function by means of the euglycemic-hyperinsulinemic clamp technique combined with an intravenous glucose tolerance test (IVGTT). After an overnight fast, blood samples were taken and a 2-h basal tracer equilibration period was initiated. The 2-h basal period was followed by a 30-min IVGTT to characterize first-phase insulin secretion. After the IVGTT, a euglycemic-hyperinsulinemic clamp at 40 mU/m^2/min for 2 h was performed for estimation of peripheral insulin sensitivity (20). A primed-constant [3-^{3}H]glucose infusion was used throughout the entire study period, and [3-^{3}H]glucose was added to the glucose infusates to maintain a constant plasma specific activity during the clamp period.

Body weight (BW) was measured to the nearest 0.1 kg with an electronic standard scale (Tanita, BWB-620A) with the participant wearing light clothes, and height was measured to the nearest 0.5 cm with the participant not wearing shoes. Total body fat and fat-free mass were determined with a bioimpedance analyzer (Biodynamics, Seattle, WA) (21). Body surface area was calculated according to the formula of DuBois and DuBois (22).

Gut glucose absorption

The details for the estimation of glucose absorption have been reported elsewhere (8). Here we summarize the description in brief. For a given BW in the post-OGTT state, the increase in circulating glucose over time ($dgluc_{circ}/dt$) is determined by the gain from gut glucose absorption and endogenous glucose production (EGP) as well as the loss because of glucose disposal (Rd). Accordingly, changes in glucose concentration over time can be expressed as follows: $dgluc_{circ}/dt = 1/V_G \times [BW \times (EGP - Rd) + ABS]$, with initial conditions of gluc(0) equal to FPG. In this equation, V_G is the oral distribution volume, which in this case is only a scaling factor assumed as 9% of BW (23). Time-dependent rates of EGP and Rd during the OGTT were estimated by a validated method (8). We used this equation to calculate gut glucose absorption (ABS in the equation).

For each participant, total glucose absorption during the OGTT was calculated by integrating glucose absorption rates across the 180-min OGTT. Glucose half-life ($T_{1/2}$) in the gastrointestinal tract (i.e., time until half of the total glucose had been absorbed from the gut) was individually determined by linear curve interpolation of the relative glucose retention during the OGTT by the closest time points to cross the 50% threshold (24).

Estimates of insulin sensitivity and β-cell function

The gold-standard estimate of peripheral insulin sensitivity was calculated as the mean glucose infusion rate per kg fat-free mass during the last 30 min of the euglycemic-hyperinsulinemic clamp (M value). In addition to this measure, we estimated insulin sensitivity from the OGTT according to commonly used surrogate markers: *1*) the Matsuda index (25), including plasma glucose and serum insulin taken at 0, 30, 60, 90, and 120 min during the OGTT; *2*) the insulin sensitivity index (ISI_{0-120}) (26), including 0- and 120-min glucose and insulin values as well as BW; and *3*) the BIGTT-SI index (16), which is calculated from glucose and insulin concentrations measured at 0, 30, and 120 min and also from sex and BMI.

A reliable and widely accepted estimate of first-phase insulin response was obtained from the IVGTT by calculating the incremental area under the serum insulin curve during the first 10 min after the glucose bolus. Surrogate markers of first-phase insulin secretion (β-cell function) were estimated from the OGTT by various methods: *1*) the insulinogenic index (27), modeling the change in serum insulin divided by the change in plasma glucose from 0 to 30 min; *2*) the Stumvoll first-phase insulin secretion index (28), which includes information on serum insulin at 0 and 30 min as well as plasma glucose at 30 min; and *3*) the BIGTT-AIR (16), which uses, in addition to sex and BMI, information on plasma glucose and serum insulin concentrations at 0, 30, and 120 min.

Laboratory analysis

Blood samples for measurement of venous plasma glucose during the OGTT and IVGTT, as well as [3-^{3}H]glucose during the clamp, were taken in a tube containing sodium fluoride and put on ice immediately. Plasma glucose was analyzed with the hexokinase and glucose-6-phosphate

dehydrogenase technique (Roche Diagnostics, Mannheim, Germany). [3-^{3}H]Glucose activity was determined from evaporated plasma samples (29). Plasma [3-^{3}H]water was determined from the activity in the plasma sample minus the activity in the same plasma sample after evaporation. During the clamp, whole blood glucose was measured on a One Touch Profile glucose meter (LifeScan, Milpitas, CA). Measurement of serum insulin was performed with the fluoroimmunoassay technique (AutoDELFIA; Perkin Elmer-Wallac, Turku, Finland).

Statistical analysis

First, we examined whether specific dimensions of glucose absorption differed among individuals of discrete glucose tolerance status (NGT vs. i-IFG vs. i-IGT). We calculated total glucose absorption, early (0–60 min) and late (60–120 min) glucose absorptions, time to peak glucose absorption, peak glucose absorption, and the velocity of glucose absorption ($T_{1/2}$). Next, we studied potential differences in glucose absorption patterns between men and women with NGT or i-IGT. Pairwise differences in dimensions of glucose absorption as well as measures of insulin sensitivity and β-cell function between groups (glucose tolerance status, sex, or both) were tested with *t* tests. We also studied associations of $T_{1/2}$ with continuously measures of FPG and 2hPG as well as with body size (height and fat-free mass) in the entire study population by means of linear regression analysis. Moreover, we examined whether differences in body size could explain any observed differences in glucose absorption patterns using linear regression models. Finally, we studied whether the OGTT-derived measures of insulin sensitivity and β-cell function also reflected the differences found between normal and impaired glucose regulation measured by the gold-standard methods and how differences in velocity of glucose absorption ($T_{1/2}$) affected the associations. All glucose absorption data, $ISI_{0–120}$, and all estimates of β-cell function were logarithmically transformed before analysis to fulfill the assumption of normality of the residuals. Statistical analyses were performed in SAS version 9.2 (SAS Institute, Inc, Cary, NC), and a two-sided 5% significance level was used.

RESULTS

Glucose absorption patterns and glucose tolerance status

Clinical characteristics and dimensions of glucose absorption in individuals with NGT, i-IFG, and i-IGT are shown in Table 1. Median glucose absorptions at 11 discrete time points during the OGTT in individuals with NGT, i-IFG, and i-IGT are shown in Fig. 1. The $T_{1/2}$ was significantly shorter in the i-IFG group compared with the NGT group ($P = 0.036$) and the i-IGT group ($P = 0.001$). Moreover, the time to peak of glucose absorption was shorter ($P = 0.013$) and late glucose absorption (60–120 min) was lower ($P = 0.011$) in participants with i-IFG than in those with NGT. Total glucose absorption also tended to be lower in those with i-IFG

Table 1—*Clinical characteristics, dimensions of glucose absorption, and estimates of insulin sensitivity and β-cell function in individuals with NGT, i-IFG and i-IGT*

	NGT (*n* = 20)	i-IFG (*n* = 18)	i-IGT (*n* = 28)	*P* value
Clinical characteristics				
Men (*n*)	11	16[a,b]	16	0.039
Age (years)	49.8 (10.6)	53.9 (7.5)	14.0 (8.2)	0.19
Height (cm)	174.7 (9.6)	176.4 (8.8)	169.9 (9.0)[b]	0.039
BMI (kg/m^2)	25.6 (3.3)	27.8 (3.6)[a]	27.9 (3.5)[c]	0.042
Waist-to-hip ratio	0.87 (0.09)	0.96 (0.07)[a]*	0.93 (0.08)[c]*	0.003
Fat-free mass (kg)	59.6 (48.5–67.1)	63.7 (55.8–76.1)[a,b]	55.3 (49.3–66.2)	0.032
FPG (mmol/L)	5.4 (0.4)	6.2 (0.3)[a]**,[b]**	5.7 (0.4)	<0.0001
2hPG (mmol/L)	6.6 (1.2)	5.7 (1.4)	8.5 (0.9)[b]**,[c]**	<0.0001
Glucose absorption patterns				
Total glucose absorption (g)	71.6 (60.5–78.2)	60.2 (40.5–75.2)	63.7 (43.3–80.7)	0.23
Early glucose absorption, 0–60 min (g)	33.5 (30.1–43.8)	34.5 (23.9–45.2)	32.0 (22.2–40.1)	0.19
Late glucose absorption, 60–120 min (g)	27.1 (22.7–30.5)	13.7 (10.8–26.8)[a,b]	24.7 (15.7–30)	0.036
Peak glucose absorption (g)	0.73 (0.64–0.86)	0.86 (0.57–1.01)	0.76 (0.55–0.93)	0.42
Time to peak (min)	30 (20–45)	20 (10–30)[a]	30 (10–45)	0.049
$T_{1/2}$ (min)	60 (55–70)	50 (40–65)[a,b]*	65 (60–75)	0.007
Estimates of insulin sensitivity				
M value (clamp, mg per kg fat-free mass)	8.9 (7.1–10.2)	8.0 (5.8–9.8)	6.2 (4.6–8.0)[c]*	0.017
Matsuda index (OGTT)	19.0 (13.2–23.2)	15.9 (10.3–20.8)	11.4 (8.7–18.8)[c]	0.042
$ISI_{0–120}$ (OGTT)	34.4 (28.2–39.4)	44.0 (36.1–48.5)	22.4 (19.0–25.8)[b]**,[c]**	<0.0001
BIGTT-SI (OGTT)	8.7 (6.7–6.7)	7.6 (6.2–6.2)	5.0 (3.7–3.7)[b]*,[c]*	0.004
Estimates of β-cell function				
FPIR (IVGTT, nmol/L)	1.6 (0.8–3.7)	1.1 (0.7–1.5)[a,b]	1.8 (1.0–2.6)	0.049
Insulinogenic index$_{30\ min}$ (OGTT)	57.8 (42.5–129.0)	67.1 (39.8–108.9)	66.5 (40.0–88.0)	0.77
Stumvoll first-phase (OGTT)	577 (460–1,001)	634 (413–986)	729 (516–1,098)	0.49
BIGTT-AIR ($\times 10^3$) (OGTT)	1.6 (1.2–2.0)	1.3 (1.0–1.6)[a,b]*	1.7 (1.4–2.5)	0.031

Data are mean (SD) or median (IQR), or proportions (95% CI), except as marked. Level of significance $P < 0.05$ except as marked. FPIR, first-phase insulin response. [a]Difference significant for i-IFG versus NGT. [b]Difference significant for i-IFG versus i-IGT. [c]Difference significant for i-IGT versus NGT. *Level of significance $P < 0.01$. **Level of significance $P < 0.0001$.

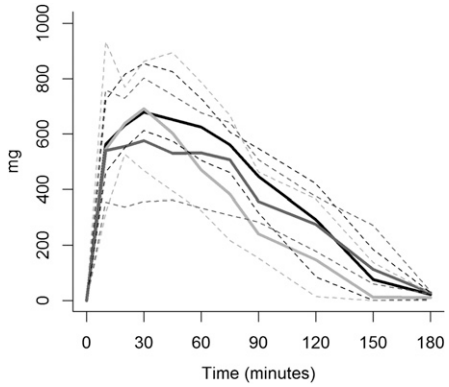

Figure 1—*Glucose absorptions during the 12-point, 3-h OGTT in individuals with NGT (black lines,* n = *20), i-IFG (light gray lines,* n = *18), and i-IGT (dark gray lines,* n = *28). Solid lines represent medians; dashed lines are IQRs.*

than in those with NGT ($P = 0.086$). The same findings were observed when only men were analyzed (data not shown). When FPG was analyzed as a continuous variable, we found an inverse relationship with $T_{1/2}$ ($P = 0.001$; Fig. 2*A*).

Early glucose absorption (0–60 min) tended to be lower in those with i-IGT than in those with NGT ($P = 0.068$) (Table 1), but other dimensions of glucose absorption did not differ between individuals with i-IGT and NGT. Nevertheless, higher 2hPG concentrations were significantly related to slower glucose absorption in the entire study population ($P = 0.001$) (Fig. 2*B*).

Glucose absorption patterns and sex differences

We found no differences in any dimensions of glucose absorption between men and women with NGT ($P \geq 0.121$ for all comparisons). Within the i-IGT group, early glucose absorption was slightly lower in women with i-IGT (median 29.9 g, interquartile range [IQR] 15.1–34.3 g) compared with men with i-IGT (median 34.6 g, IQR 27.0–44.2 g; $P = 0.041$). Also, peak glucose absorption was lower in women with i-IGT (median 0.62 g, IQR 0.36–0.79 g) than in men with i-IGT (median 0.80 g, IQR 0.58–0.98 g; $P = 0.015$). In addition, $T_{1/2}$ tended to be longer in women with i-IGT (median 72.5 min, IQR 65–77.5 min) than in their male counterparts (median 65.0 min, IQR 60.0–70.0 min; $P = 0.096$), indicating a slower glucose absorption. No other dimensions of glucose absorption differed by sex within the i-IGT group ($P \geq 0.205$ for all other comparisons).

Glucose absorption patterns and body size

The velocity of glucose absorption ($T_{1/2}$) was inversely associated with both height and the amount of fat-free mass ($P < 0.001$) (Fig. 2*C* and *D*). We therefore subsequently adjusted all analyses for height or fat-free mass together with age. In the adjusted analyses, late glucose absorption was still significantly lower in the i-IFG group than in the NGT group ($P < 0.01$), and $T_{1/2}$ and time to peak were significantly shorter in the i-IFG group than in both the i-IGT ($P < 0.05$) and NGT ($P < 0.05$) groups. All significant differences between men and women within the i-IGT group disappeared after adjustment for age and height or fat-free mass ($P \geq 0.22$ for all). The relationships of $T_{1/2}$ with FPG and 2hPG concentrations were slightly attenuated but remained significant after adjustment for age and height or fat-free mass ($P < 0.022$ for all).

Insulin sensitivity and β-cell function values obtained from gold-standard versus OGTT measures

Individuals with i-IGT had 30% reduced peripheral insulin sensitivity compared with the NGT group when evaluated with the euglycemic hyperinsulinemic clamp ($P = 0.003$). This difference was captured by all the OGTT-derived measures, with differences in insulin sensitivity between the i-IGT group and the NGT group of 33% for the Matsuda index ($P = 0.012$), 41% for ISI_{0-120} ($P < 0.001$), and 43% for BIGTT-SI ($P = 0.002$) (Table 1). Adjustment for $T_{1/2}$ did not change these findings ($P \leq 0.001$ for all).

The i-IFG group had 42% lower first-phase insulin response than did the NGT group when estimated from the IVGTT ($P = 0.026$). This difference was also found with the BIGTT-AIR index derived from the OGTT (34% lower in i-IFG vs. NGT; $P = 0.037$) (Table 1). We did not, however, find a significantly lower mean β-cell function for i-IFG versus NGT when evaluated by the insulinogenic index (13% lower; $P = 0.728$) or the Stumvoll index (7% lower; $P = 0.626$). Adjustment for $T_{1/2}$ resulted in larger mean differences in the insulinogenic index (22% lower in i-IFG vs. NGT) and the Stumvoll index (16% lower in i-IFG vs. NGT); however, the differences were still not significant ($P \geq 0.23$). The BIGTT-AIR index was 38% lower in subjects with i-IFG than in those with NGT after adjustment for $T_{1/2}$ ($P = 0.008$).

CONCLUSIONS—In this study, we hypothesized that glucose absorption patterns might differ between men and women with normal and impaired glucose regulation and that such differences may affect the estimation of insulin sensitivity and insulin secretion from OGTTs. Our data showed that individuals with i-IFG had faster glucose absorption during the OGTT than did those with NGT, as indicated by an earlier peak of glucose absorption and a shorter $T_{1/2}$. In contrast, individuals with i-IGT did not exhibit a significantly different glucose absorption pattern from those with NGT. Women with i-IGT did have slower glucose absorption than did their male counterparts; however, this difference was explained by differences in body size between men and women. We also found that estimates of insulin sensitivity from OGTTs resembled those measured by gold-standard techniques, although two of three surrogate markers of β-cell function did not capture the β-cell dysfunction observed in i-IFG when a gold-standard method (IVGTT) was used.

Several studies have shown that the pathophysiologic mechanisms underlying the prediabetic states i-IFG and i-IGT differ widely (18,19,30,31); however, this is the first study to show that the glucose absorption pattern in response to an OGTT among individuals with i-IFG is different from that among those with NGT and i-IGT. The faster glucose absorption rate in addition to the normal peripheral insulin sensitivity observed in those with i-IFG may contribute to their ability to obtain normal 2hPG concentrations. Despite the faster glucose absorption in the i-IFG group, early glucose absorption (0–60 min) did not differ between the groups. The reason may be that the i-IFG group had an earlier peak followed by a steeper decline of glucose absorption toward 60 min relative to the other groups (Fig. 1), resulting in similar total glucose absorption rates in the three groups during the first hour. In support of the faster glucose absorption in the i-IFG group, we found that the velocity of glucose absorption was related to the FPG concentration. This information is important when the OGTT is used for diagnosis of diabetes, because faster early glucose absorption may result in lower 2hPG levels. Abnormal glucose absorption patterns during OGTT in patients with type 2 diabetes and gestational diabetes mellitus (12,13) may therefore partly explain the lack of overlap in the diagnosis of

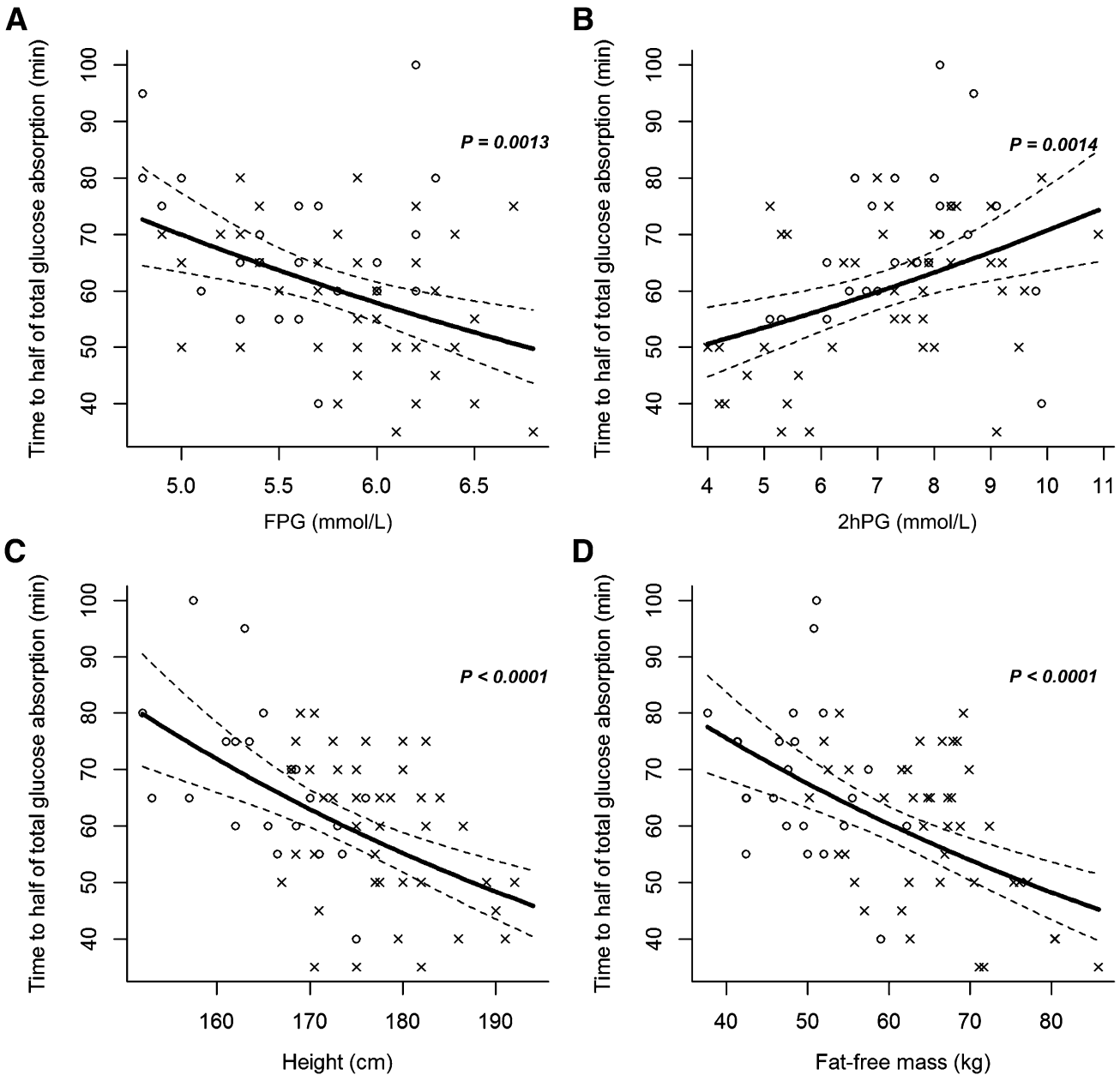

Figure 2—*Associations of the velocity of glucose absorption ($T_{1/2}$) with FPG (A), 2hPG (B), height (C), and fat-free mass (D) in men (×) and women (○). Solid lines represent estimated values; dashed lines are 95% CIs.*

diabetes when using the OGTT versus HbA_{1c} criteria (32).

We found that all sex differences within the i-IGT group disappeared after adjustment for height, fat-free mass, or both. An explanation for the slower and lower early glucose absorption in women with i-IGT is thus that women in general receive a relatively larger glucose load than men (because of their smaller body size). Our finding of significantly slower glucose absorption ($T_{1/2}$) in individuals with short height and low fat-free mass, as well as our previous observations (3), support this notion. In other words, the ability to absorb and metabolize a standard OGTT seems to differ according to stature.

The OGTT-derived estimates of insulin sensitivity reflected the differences found by the glucose clamp technique between individuals with NGT and those with i-IGT. Although the OGTT-derived indices of insulin sensitivity have been developed from or validated against the clamp (16,25,26), the finding was unexpected because a previous study predicted pronounced increments of OGTT-derived indices of insulin sensitivity (i.e., reduced insulin resistance) if intestinal glucose absorption was simulated to be reduced by 50% (11). Together, these findings illustrate that conclusions derived from simulation models of glucose and insulin kinetics are not always in agreement with real-life conditions. With respect to β-cell function, only the BIGTT-AIR index was useful in expressing the abnormality in first-phase insulin response characteristic of those with i-IFG. This index may be superior to the other two indices because it is derived from a tolbutamide-modified,

frequently sampled IVGTT and also includes information on sex and body size (16). The main difference between insulin secretion during OGTT and IVGTT—aside from glucose absorption patterns—is the incretin effect, which is only activated during oral glucose ingestion. The BIGTT-AIR index thus seems to bypass differences in both glucose absorption and incretin hormones, thereby expressing an index of insulin secretion independent of orally induced factors, even though it is based on an OGTT. Adjustment for the velocity of glucose absorption slightly improved the performance of the insulinogenic index and the Stumvoll index, although not sufficiently. Future development of new models for assessing β-cell function on the basis of more physiologically relevant tests (e.g., meal tests) seems relevant to cover real-life aspects of pancreatic β-cell function.

The major strength of this study was the combination of OGTT, IVGTT, and clamp data, enabling a direct comparison of OGTT-derived measures with gold-standard measurements of insulin sensitivity and insulin secretion. We used the World Health Organization criteria for categorizing individuals into the discrete prediabetic groups, and these criteria have a higher cutoff point for i-IFG than that suggested by the American Diabetes Association. However, we did find linear relationships of the velocity of glucose absorption with both FPG and 2hPG concentrations when analyzed as continuous variables, so it is unlikely that the use of the American Diabetes Association criteria would yield very different results, even though the distribution of participants in the various groups would be different. A major limitation of our study was that glucose absorption was not measured directly but estimated by our validated method; however, FPG and 2hPG levels only contribute a small fraction to the estimation of the various dimensions of glucose absorption, limiting the possibility of overlap with the classification of the prediabetic groups. Another limitation was that glucose effectiveness (glucose-mediated glucose uptake and inhibition of EGP) was not taken into account in the glucose absorption model because it significantly blurred the shape of the absorption curve (8). At high blood glucose concentrations during the OGTT, glucose effectiveness would reduce EGP and increase peripheral Rd slightly. In general, individuals with impaired glucose regulation (including diabetes) have lower glucose effectiveness than do those with NGT (33). Because inclusion of glucose effectiveness in the glucose absorption model gave a deviation of 10% at most (8), however, we believe that our conclusions would not have been changed had we included glucose effectiveness in the estimation.

Unfortunately, the relatively small study size limited a detailed study of potential interactions among sex, glucose tolerance status, and glucose absorption. The presented results therefore should be interpreted with caution and need replication in other independent datasets.

In conclusion, we found glucose absorption patterns to be abnormal in prediabetic individuals with i-IFG. The velocity of glucose absorption was inversely associated with 2hPG levels and positively associated with FPG levels and body size. A tall person or one with high FPG (i.e., i-IFG) will on average have a faster glucose absorption during an OGTT, and thus lower 2hPG levels, than a shorter person or one with lower FPG. These differences are likely to affect the estimation of β-cell function by OGTT, as well as the diagnosis of diabetes and prediabetic conditions. Despite the close linkage of glucose absorption patterns, plasma glucose levels, and body size shown in this study, more studies are needed before information on differences in glucose absorption can be used in the treatment of patients with diabetes.

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K.F. collected data and wrote first draft with major input from D.V. G.P. and A.T. calculated glucose absorption parameters. K.F. and D.V. performed the statistical analyses. J.J.N. and T.H. reviewed and edited the manuscript. All authors critically reviewed and approved the manuscript before submission. K.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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