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Different pathophysiology of impaired glucose tolerance in first-degree relatives of individuals with type 2 diabetes mellitus

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Abstract

To assess whether an increased genetic predisposition for type 2 diabetes mellitus (T2DM) influences the contributions of insulin resistance and impaired insulin secretion to impaired glucose tolerance (IGT), 437 subjects not known to have T2DM underwent an oral glucose tolerance test and a 3-hour hyperglycemic clamp. Plasma insulin responses and insulin sensitivity were compared between all subjects (unselected for demographic or anthropometric characteristics) who had normal glucose homeostasis and no first-degree T2DM relative (n = 133), IGT with a first-degree T2DM relative (IGT/FH+, n = 74), or IGT without a first-degree T2DM relative (IGT/FH−, n = 50). Compared with those with normal glucose homeostasis, first- and second-phase plasma insulin responses were reduced approximately 45% and 30%, respectively (both $P < .001$), in IGT/FH+, whereas insulin sensitivity was only approximately 20% reduced ($P = .011$). In contrast, in IGT/FH−, first-phase plasma insulin responses were only approximately 20% reduced ($P = .016$), second-phase plasma insulin responses were not reduced, but insulin sensitivity was approximately 40% reduced ($P < .001$). The IGT/FH+ group differed significantly from the IGT/FH− group by having 25% to 30% lower first-phase plasma insulin responses ($P = .026$) and 25% to 30% greater insulin sensitivity ($P = .027$). Adjustment for obesity abolished the differences in insulin resistance but not plasma insulin responses. However, when the IGT groups were stratified into subgroups based on body mass index (BMI), first-phase plasma insulin responses were approximately 30% lower in IGT/FH+ with a BMI of at least 27 kg/m^2 ($P = .018$) but similar in IGT/FH+ with a BMI less than 27 kg/m^2 compared with the corresponding IGT/FH− subgroups. We conclude that, in IGT, an increased genetic predisposition for T2DM increases the contribution of impaired insulin secretion to its pathophysiology. This effect is enhanced by obesity.
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1. Introduction

Impaired glucose tolerance (IGT) is an intermediate glycemic state between normality and type 2 diabetes mellitus (T2DM) [1]. Like T2DM, it is due to a combination of impaired insulin secretion and insulin resistance; but the extent by which each of these defects contributes to the abnormal glucose homeostasis may differ substantially between individuals [1-3]. Because IGT precedes and increases the risk for T2DM [4], therapeutic strategies to halt/slow progression of IGT to T2DM are important and should target the predominant correctable underlying defect.

In normal glucose-tolerant individuals who were either the first-degree relative of someone with T2DM or who had an identical twin with T2DM, most studies have found impairment in insulin secretion but less evidence for insulin resistance when factors such as age, sex, obesity, and body fat distribution have been taken into consideration [5]. Thus, in normal glucose-tolerant individuals, a strong genetic predisposition for T2DM seems to be primarily associated with β-cell dysfunction. However, whether an increased

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genetic predisposition for T2DM has a similar association in people with IGT is unclear.

In the present study, we therefore used the hyperglycemic clamp technique and compared insulin secretion and insulin sensitivity in a large number of normal glucose-tolerant subjects, IGT subjects with a first-degree T2DM relative, and IGT subjects without a first-degree T2DM relative.

2. Materials and methods

2.1. Subjects

We have systematically collected data from 437 individuals not known to have T2DM who underwent a standard oral glucose tolerance test (OGTT) and a hyperglycemic clamp between 1986 and 2006. For inclusion, subjects had to be 18 to 70 years of age and in good health, and had to have normal physical examination result and normal routine laboratory test result. Subjects taking medications known to affect glucose metabolism were excluded. Out of the 437 subjects, 127 were found to have *IGT* defined as a 2-hour postchallenge plasma glucose concentration greater than or equal to 140 mg/dL and less than 200 mg/dL [6]. Out of these, 74 subjects reported having at least 1 first-degree T2DM relative (IGT/FH+); and 50 subjects reported having no first-degree T2DM relative (IGT/FH−). Three subjects reported that they had been adopted so that no information on their family history of T2DM was available. All subjects who were found to have normal glucose homeostasis (fasting plasma glucose <100 mg/dL, 2-hour postprandial plasma glucose <140 mg/dL) and a negative family history of T2DM (n = 133) served as controls. Information regarding family history of T2DM was specifically explored during the screening history and physical. Out of the 257 subjects included in the present analyses, 131 were studied in the United States, 54 in Brazil, 35 in the Netherlands, 14 in Italy, 13 in Greece, and 10 in Finland. All subjects gave informed written consent after the local Institutional Review Board had approved the protocol. The results of the hyperglycemic clamps of some subjects have been included in previous reports [7-11].

2.2. Protocol

Hyperglycemic clamps were performed as previously described [7-11]. All subjects had been on a weight-maintaining diet and had abstained from alcohol and strenuous exercise for 3 days before the study. After an overnight fast, a dorsal hand vein was cannulated in a retrograde fashion and kept in a thermoregulated Plexiglas box at 65°C for sampling arterialized venous blood [12]. An antecubital vein was cannulated for infusion of 20% glucose. After a 30-minute baseline period (−30 to 0 minute), a primed (150 mg/kg body weight) 20% glucose infusion was given to raise plasma glucose concentrations acutely to 10 mmol/L. Plasma glucose concentrations were subsequently maintained at 10 mmol/L for 180 minutes by a variable 20% glucose infusion using the glucose clamp technique, with plasma glucose concentrations measured at 5-minute intervals [13]. Blood samples for plasma insulin determinations were obtained at −30, −15, 0, 2.5, 5, 7.5, 10, 20, 40, 60, 80, 100, 120, 140, 160, and 180 minutes.

2.3. Analytical procedures

Plasma glucose concentrations were determined by a glucose analyzer (YSI Glucose Analyzer [YSI, Inc, Yellow Springs, OH] or Beckman Glucose Analyzer [Beckman Instruments, Fullerton, CA]). Plasma insulin concentrations were determined using human insulin-specific radioimmunoassay (Pharmacia Insulin RIA; Kabi Pharmacia Diagnostics, Piscataway, NJ, or Linco Insulin RIA; Linco Research, St Charles, MO).

2.4. Calculations

The area under the curve (AUC) of plasma glucose concentrations during the OGTT was calculated by the trapezoidal rule. First-phase plasma insulin responses were calculated as the average incremental plasma insulin concentration at 2.5, 5.0, 7.5, and 10 minutes of the hyperglycemic clamp divided by the average incremental plasma glucose concentration during the same interval. Second-phase plasma insulin responses were calculated as the average incremental plasma insulin concentration during the last hour of the hyperglycemic clamp divided by the average incremental plasma glucose concentration during the same interval [11]. Insulin sensitivity was determined by dividing the average glucose infusion rate during the last hour of the hyperglycemic clamp by the average plasma insulin concentration during the same interval [13], referred to as the *insulin sensitivity index* (ISI). The ISI was multiplied by the ratio of 180 mg/dL to the actual plasma glucose concentration in milligrams per deciliter during the hyperglycemic clamp to account for small differences in plasma glucose concentrations. In individuals with normal glucose homeostasis, decreased insulin sensitivity is associated with increased insulin secretion so that the product of both of these processes, referred to as the *disposition index* (DI), is similar to that of subjects with normal insulin sensitivity [14]. Therefore, to evaluate the appropriateness of insulin secretion in relation to insulin sensitivity, we calculated the DI of the first- (DI first phase) and second-phase plasma insulin response (DI second phase) by multiplying the respective insulin responses with the ISI [14].

2.5. Statistical analyses

Body mass index (BMI), second-phase insulin responses, ISI, DI first phase, and DI second phase were log-transformed to obtain a normal distribution of the data for statistical analyses. Continuous variables were compared between groups using analysis of variance (ANOVA) followed by the least significant difference test for variables for which the F test was significant; categorical variables, that is, sex, were compared using the χ^2 test. In addition,

metabolic data were compared between groups by analysis of covariance (ANCOVA) with age, sex, BMI, and waist-to-hip ratio (WHR) as covariates.

Normally distributed variables are given as means ± SE. For skewed data, geometric means and 95% confidence intervals are given. All analyses were conducted using the SPSS 15.0 (SPSS, Chicago, IL). *P* values less than .05 were considered statistically significant.

3. Results

3.1. Demographic and anthropometric characteristics

Age, sex, BMI, and WHR were significantly different between the control group, the IGT/FH+ group, and the IGT/FH− group as indicated by ANOVA and χ^2 tests (all $P < .02$) (Table 1). Compared with the control group, IGT/FH+ and IGT/FH− were older and had a greater BMI and WHR (all $P < .001$); and IGT/FH− ($P < .005$) but not IGT/FH+ had a higher male-to-female ratio. The IGT/FH+ group differed significantly from the IGT/FH− group by having a lower WHR ($P < .007$).

Fasting and 2-hour postprandial plasma glucose concentrations during the OGTT as well as AUC glucose during the OGTT were significantly increased in IGT/FH+ and IGT/FH− (all $P < .001$) but similar among each other (all $P > .2$). The proportion of subjects who had impaired fasting glucose was also similar in IGT/FH+ and IGT/FH− (42% vs 48%, $P > .6$).

3.2. Hyperglycemic clamp

During the hyperglycemic clamp, plasma glucose increased to comparable levels in all 3 groups (Fig. 1, Tables 2 and 3). However, the increment in plasma glucose concentrations was slightly (by ~0.5 mmol/L) but similarly lower in both IGT groups compared with the control group (both $P < .01$). For evaluation of first- and second-phase plasma insulin responses, increments in plasma insulin concentrations were therefore divided by the increments in plasma glucose concentrations as described above to adjust for the slightly different glycemic stimuli for insulin secretion. The ANOVA indicated significant differences between the 3 groups for first-phase plasma insulin responses, second-phase plasma insulin responses, ISI, and both DIs (all $P < .003$).

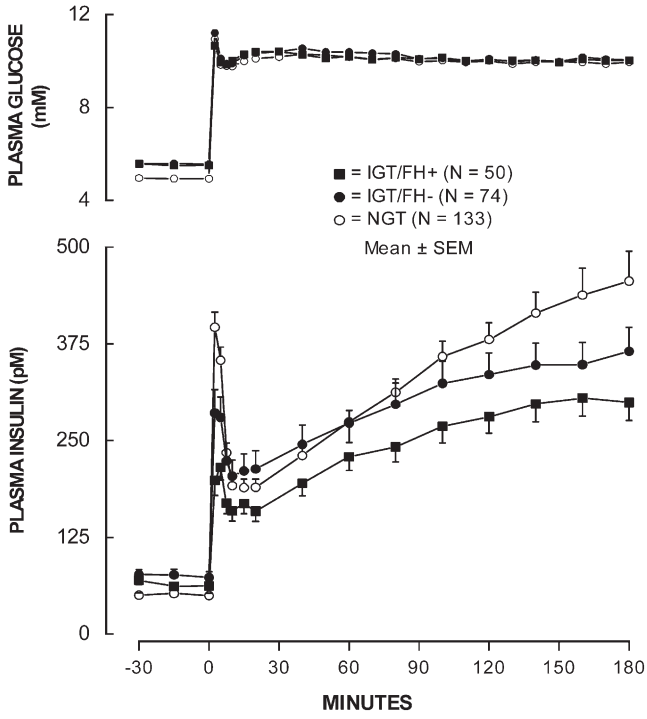

Fig. 1. Plasma concentrations of glucose and insulin during the hyperglycemic clamp in IGT/FH+, IGT/FH−, and subjects with normal glucose tolerance. NGT indicates normal glucose tolerance.

Compared with the control group, IGT/FH+ had approximately 45% reduced first-phase plasma insulin responses ($P < .001$), approximately 30% reduced second-phase plasma insulin response ($P < .001$), and approximately 20% reduced ISI ($P = .011$). Accordingly, DI first phase and DI second phase were reduced by approximately 59% and 43%, respectively (both $P < .001$). In contrast, in IGT/FH−, first-phase plasma insulin responses were only approximately 20% reduced ($P = .016$), second-phase plasma insulin responses were not significantly reduced (~15% reduction, $P = .16$), and ISI was approximately 40% reduced ($P < .001$). Accordingly, DI first phase and DI second phase were reduced by approximately 59% and 47%, respectively (both $P < .001$).

Table 1
Demographic and anthropometric characteristics of the study population and results of the OGTTs

	IGT/FH+ (1)	IGT/FH− (2)	Controls (3)	*P* value		
				1 vs 2	1 vs 3	2 vs 3
Age (y)	48.7 ± 1.4	50.4 ± 1.6	41.0 ± 1.0	>.4	<.001	<.001
Sex (M/F)	26/48	25/25	36/97	=.10	>.2	<.005
BMI (kg/m^2)	27.7 (26.5-29.0)	28.9 (27.7-30.1)	25.7 (25.1-26.3)	=.17	<.001	<.001
WHR	0.86 ± 0.01	0.90 ± 0.01	0.82 ± 0.01	<.007	<.001	<.001
Fasting plasma glucose (mmol/L)	5.55 ± 0.06	5.60 ± 0.08	4.88 ± 0.03	>.5	<.001	<.001
2-h plasma glucose (mmol/L)	8.96 ± 0.10	9.02 ± 0.14	5.72 ± 0.08	>.7	<.001	<.001
AUC plasma glucose (mmol/L·h)	7.59 ± 0.23	7.15 ± 0.24	3.32 ± 0.16	>.2	<.001	<.001

Data are means ± SE. Body mass index is given in geometric means (95% confidence interval).

Table 2
Results from the hyperglycemic clamp test

	IGT/FH+ (1)	IGT/FH− (2)	Controls (3)	*P* value		
				1 vs 2	1 vs 3	2 vs 3
1st-phase insulin secretion (pmol/L)/(mmol/L)	26.3 ± 2.2	36.8 ± 4.1	47.2 ± 2.3	=.026	<.001	=.016
2nd-phase insulin secretion (pmol/L)/(mmol/L)	43.0 (36.5-50.8)	51.3 (42.5-62.0)	60.0 (53.8-66.8)	=.148	<.001	=.157
ISI (μmol·kg^{-1}·min^{-1}·[pmol/L]$^{-1}$)	0.114 (0.097-0.133)	0.089 (0.075-0.105)	0.142 (0.129-0.157)	= .027	= .011	<.001
DI, 1st phase (μmol·kg^{-1}·min^{-1}·[mmol/L]$^{-1}$)	2.35 (2.01-2.75)	2.35 (1.95-2.84)	5.67 (5.05-6.37)	>.9	<.001	<.001
DI, 2nd phase (μmol·kg^{-1}·min^{-1}·[mmol/L]$^{-1}$)	4.89 (4.45-5.38)	4.56 (4.02-5.16)	8.53 (7.96-9.14)	>.3	<.001	<.001

Data of first-phase insulin secretion are means ± SE. Other data are geometric means (95% confidence interval).

When both IGT groups were compared with one another, IGT/FH+ differed significantly from IGT/FH− by having a 25% to 30% lower first-phase plasma insulin response (P = .026) but a 25% to 30% greater ISI (P = .027). Differences in the second-phase plasma insulin response did not reach statistical significance (P = .15). Similar statistical results were obtained when increments in plasma insulin responses unadjusted for increments in plasma glucose concentrations were compared (P = .013 for first-phase plasma insulin response, P = .12 for second-phase plasma insulin response). The DI first phase and DI second phase were comparable in both groups, consistent with both groups having similar glucose tolerance.

Using ANCOVA, adjustment for age, sex, BMI, and WHR had little influence on first- and second-phase plasma insulin responses so that the statistical results of these parameters remained similar. Adjustment for age and sex also had little influence on ISI (data not shown). However, after further adjustment for BMI and WHR, ISI was no longer significantly different between the 3 groups (P > .2), suggesting that the differences in insulin sensitivity were largely due to differences in obesity.

3.3. Effect of obesity on the influence of a family history of T2DM on plasma insulin responses in IGT

Evidence indicates that subjects with a strong family history of T2DM are uniquely susceptible to impaired β-cell function by a sustained increase in plasma free fatty acid (FFA) concentrations [15]. Therefore, to assess whether obesity affects the influence of a family history of T2DM on plasma insulin responses in IGT, we stratified IGT/FH+ and IGT/FH− into subgroups with a BMI less than 27 kg/m^2 (n = 37 and n = 21, respectively) and a BMI of at least 27 kg/m^2 (n = 37 and n = 29, respectively) and compared the respective subgroups using unpaired Student t tests. In the subgroups with a BMI less than 27 kg/m^2, first- (21.7 ± 2.6 vs 23.8 ± 3.8 [pmol/L]/[mmol/L], P > .6) and second-phase plasma insulin responses (29.5 [23.9-36.4] vs 33.8 [25.6-44.7] [pmol/L]/[mmol/L], P > .4) were not significantly different between IGT/FH+ and IGT/FH−. In contrast, in the subgroups with a BMI of at least 27 kg/m^2, first-phase plasma insulin responses were more than 30% lower in IGT/FH+ than IGT/FH− (31.0 ± 3.4 vs 46.2 ± 5.9 [pmol/L]/[mmol/L], P = .018); second-phase plasma insulin responses were not statistically different (62.8 [52.4-75.3] vs 69.5 [56.6-85.1] [pmol/L]/[mmol/L], P > .4).

4. Discussion

Impaired glucose tolerance is due to a combination of insulin resistance and an inability of insulin secretion to fully compensate for the insulin resistance, which may at least in part be genetically determined. Using the hyperglycemic clamp technique in a relatively large number of subjects, the present study demonstrates that an increased genetic predisposition for T2DM, as reflected by the presence of a first-degree T2DM relative, significantly influences the contributions of both of these processes. Compared with normal glucose-tolerant subjects, IGT subjects with a first-degree T2DM relative had approximately 45% reduced first-phase plasma insulin responses and approximately 30% reduced second-phase plasma insulin responses, whereas insulin sensitivity was only approximately 20% reduced. In contrast, IGT subjects without a first-degree T2DM relative had

Table 3
Results from the hyperglycemic clamp test adjusted for age, sex, BMI, and WHR using ANCOVA

	IGT/FH+ (1)	IGT/FH− (2)	Controls (3)	*P* value		
				1 vs 2	1 vs 3	2 vs 3
1st-phase insulin secretion (pmol/L)/(mmol/L)	25.8 ± 2.8	34.7 ± 3.6	48.2 ± 2.2	=.047	<.001	<.002
2nd-phase insulin secretion (pmol/L)/(mmol/L)	43.5 (37.2-50.7)	52.2 (43.3-63.1)	59.3 (52.7-66.7)	>.5	<.001	<.001
ISI (μmol·kg^{-1}·min^{-1}·[pmol/L]$^{-1}$)	0.114 (0.099-0.132)	0.090 (0.075-0.106)	0.141 (0.127-0.157)	–[a]	–[a]	–[a]
DI, 1st phase (μmol·kg^{-1}·min^{-1}·[mmol/L]$^{-1}$)	2.49 (2.14-2.90)	2.74 (2.26-3.32)	5.18 (4.61-5.82)	>.4	<.001	<.001
DI, 2nd phase (μmol·kg^{-1}·min^{-1}·[mmol/L]$^{-1}$)	4.97 (4.52-5.46)	4.68 (4.16-5.26)	8.38 (7.80-8.99)	>.5	<.001	<.001

Data of first-phase insulin secretion are means ± SE. Other data are geometric means (95% confidence interval).

[a] F test not significant.

approximately 40% reduced insulin sensitivity, but only approximately 20% reduced first-phase plasma insulin responses and no significant reduction in second-phase plasma insulin responses. Moreover, in direct comparisons, IGT/FH+ differed significantly from IGT/FH− by having a 25% to 30% lower first-phase plasma insulin response (P = .026) but a 25% to 30% greater insulin sensitivity (P = .027). Thus, in IGT individuals with a first-degree T2DM relative, impaired insulin secretion rather than insulin resistance played the major role, whereas in IGT individuals without a first-degree T2DM relative, insulin resistance rather than impaired insulin secretion played the major role. These findings suggest that individuals with an increased genetic predisposition for T2DM may develop abnormal glucose homeostasis with less severe insulin resistance because of a greater reduction in the ability of insulin secretion to compensate for insulin resistance. This may have implications not only regarding strategies for the prevention of T2DM but also regarding its risk because progression of IGT to T2DM was linked to a greater defect to insulin secretion than insulin sensitivity at baseline in prospective studies [16,17].

In agreement with several previous reports in which IGT and normal glucose-tolerant subjects were matched for demographic and anthropometric characteristics [18-21], we found that IGT subjects had β-cell dysfunction but no insulin resistance independently of differences in obesity, estimated by BMI and WHR. Similarly, we found that the greater insulin sensitivity in the IGT/FH+ group compared with the IGT/FH− group was largely explained by differences in obesity.

For the present report, we purposely did not match groups of subjects for demographic and anthropometric characteristics but rather used data of all subjects who were found to have normal glucose homeostasis or IGT in whom information on family history of T2DM was available. This approach not only increases statistical power but also minimizes selection bias. Moreover, it does not remove or blunt characteristics that typically reflect these populations. For example, if we had matched our groups of subjects for obesity including BMI and WHR, we would not have found significant differences in insulin sensitivity between the control and IGT groups and the IGT/FH+ and the IGT/FH− groups because insulin sensitivity was no longer significantly different when adjusted for obesity using ANCOVA.

Recently, Kashyap et al [15] demonstrated that a sustained increase in plasma FFA concentrations by 4-day lipid infusion decreases insulin secretion in normal glucose-tolerant subjects with a strong family history of T2DM but increases insulin secretion in normal glucose-tolerant subjects without a family history of T2DM. Moreover, Cusi et al [22] and Paolisso et al [23] have shown that a reduction in plasma FFA levels with the antilipolytic agent acipimox for 2 to 7 days increased first-phase plasma insulin responses in nondiabetic individuals with a first-degree T2DM relative. In subanalyses of our data, we therefore tested the hypothesis that obesity affects the genetic influence on β-cell function in IGT by stratification of the IGT groups into subgroups using a BMI of 27 kg/m^2 as a cut point. Consistent with these earlier studies that altered plasma FFA concentrations [15,22,23], we found that first-phase plasma insulin responses were approximately 30% lower in IGT/FH+ with a BMI of at least 27 kg/m^2 (P = .018) but similar in IGT/FH− with a BMI less than 27 kg/m^2 compared with the corresponding IGT/FH− subgroups, suggesting that obesity might have aggravated or even precipitated the negative effects of an increased genetic predisposition for T2DM on insulin secretion in IGT/FH+.

In summary, the present study demonstrates that an increased genetic predisposition for T2DM in IGT, reflected by the presence of a first-degree T2DM relative, increases the contribution of impaired insulin secretion in its pathophysiology. This effect appears to be aggravated or even precipitated by obesity.

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