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Different Pathophysiology of Impaired Glucose Tolerance in First Degree Relatives of Individuals with Type 2 Diabetes

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Abstract

To assess whether an increased genetic predisposition for type 2 diabetes (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 OGTT and a 3-hour hyperglycemic clamp. Plasma insulin responses and insulin sensitivity were compared between all subjects (unselected for demographic or anthropometric characteristics) that had normal glucose homeostasis and no first degree T2DM relative (NGH; 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 to NGH, first and second phase plasma insulin responses were reduced ~45% and 30%, respectively (both P<0.001) in IGT/FH+, whereas insulin sensitivity was only ~20% reduced (P=0.011). In contrast, in IGT/FH-, first phase plasma insulin responses were only ~20% reduced (P=0.016), second phase plasma insulin responses were not reduced, but insulin sensitivity was ~40% reduced (P<0.001). IGT/FH+ differed significantly from IGT/FH- by having 25–30% lower first phase plasma insulin responses (P=0.026) and 25–30% greater insulin sensitivity (P=0.027). 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 ~30% lower in IGT/FH+ with a BMI ≥27 kg/m² (P=0.018) but similar in IGT/FH+ with a BMI <27 kg/m² compared to 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.

Key Terms

impaired glucose tolerance; insulin resistance; insulin secretion

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INTRODUCTION

Impaired glucose tolerance (IGT) is an intermediate glycemic state between normality and type 2 diabetes (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 contribute to the abnormal glucose homeostasis may differ substantially between individuals [1–3]. Since IGT precedes and increases the risk for type 2 diabetes (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, the majority of studies have found impairment in insulin secretion but less evidence for insulin resistance when factors such as age, gender, 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 beta-cell dysfunction. However, whether an increased 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.

MATERIALS AND METHODS

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 a normal physical examinations and normal routine laboratory tests. 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-h post-challenge plasma glucose concentration between ≥ 140 and < 200 mg/dl [6]. Out of these, 74 subjects reported having at least one 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 that 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 U.S., 54 in Brazil, 35 in 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].

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 three days prior to the study. After an overnight fast, a dorsal hand vein was cannulated in a retrograde fashion and kept in a thermoregulated Plexiglass box at 65°C for sampling arterialized venous blood [12]. An antecubital vein was cannulated for infusion of 20% glucose. After a 30 min baseline period (–30 to 0 min), a primed (150 mg/kg bodyweight) 20% glucose infusion was

given to raise plasma glucose concentrations acutely to 10 mM. Plasma glucose concentrations were subsequently maintained at 10 mM 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 min.

Analytical Procedures

Plasma glucose concentrations were determined by a glucose analyzer (YSI Glucose Analyzer or Beckman Glucose Analyzer). 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).

Calculations

The area under the curve 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 mg/dl 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, 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 Disposition Index of the first (DI 1st phase) and second phase plasma insulin response (DI 2nd phase) by multiplying the respective insulin responses with the ISI [14].

Statistical Analyses

Body mass index (BMI), second phase insulin responses, ISI, DI 1st phase, and DI 2nd phase were log-transformed to obtain a normal distribution of the data for statistical analyses. Continuous variables were compared between groups using ANOVA followed by the Least Significant Difference Test for variables for which the F-test was significant; categorical variables, i.e. gender, were compared using the chi squared (χ^2) test. In addition, metabolic data were compared between groups by Analysis of Covariance (ANCOVA) with age, gender, BMI, and waist-to-hip ratio (WHR) as covariates.

Normally distributed variables are given as means $\pm$ SE. For skewed data, geometric means and 95% confidence intervals are given. All analyses were conducted using the Statistics Package for Social Science (SPSS 15.0, SPSS Inc.). P values <0.05 were considered statistically significant.

RESULTS

Demographic and Anthropometric Characteristics (Table 1)

Age, gender, BMI and WHR were significantly different between the control group, the IGT/FH+ group and the IGT/FH- group as indicated by ANOVA and chi squared tests (all P<0.02).

Compared to the control group, IGT/FH+ and IGT/FH- were older, and had a greater BMI and WHR (all $P < 0.001$), and IGT/FH- ($P < 0.005$) but not IGT/FH+ had a higher male-to-female ratio. IGT/FH+ differed significantly from IGT/FH- by having a lower WHR ($P < 0.007$).

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 $P < 0.001$) but similar amongst each other (all $P > 0.2$). The proportion of subjects that had Impaired Fasting Glucose was also similar in IGT/FH+ and IGT/FH- (42% vs 48%, $P > 0.6$).

Hyperglycemic Clamp (Figure 1, Tables 2 and 3)

During the hyperglycemic clamp, plasma glucose increased to comparable levels in all three groups. However, the increment in plasma glucose concentrations was slightly (by ~0.5 mM) but similarly lower in both IGT groups compared to the control group (both $P < 0.01$). 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. ANOVA indicated significant differences between the three groups for first phase plasma insulin responses, second phase plasma insulin responses, ISI, and both Disposition Indices (all $P < 0.003$).

Compared to the control group, IGT/FH+ had approximately 45% reduced first phase plasma insulin responses ($P < 0.001$), approximately 30% reduced second phase plasma insulin response ($P < 0.001$), and approximately 20% reduced ISI ($P = 0.011$). Accordingly, DI 1st phase and DI 2nd phase were reduced by approximately 59 and 43%, respectively (both $P < 0.001$). In contrast, in IGT/FH-, first phase plasma insulin responses were only approximately 20% reduced ($P = 0.016$), second phase plasma insulin responses were not significantly reduced (~15% reduction, $P = 0.16$), and ISI was approximately 40% reduced ($P < 0.001$). Accordingly, DI 1st phase and DI 2nd phase were reduced by approximately 59 and 47%, respectively (both $P < 0.001$).

When both IGT groups were compared with one another, IGT/FH+ differed significantly from IGT/FH- by having a 25–30% lower first phase plasma insulin response ($P = 0.026$) but a 25–30% greater ISI ($P = 0.027$). Differences in the second phase plasma insulin response did not reach statistical significance ($P = 0.15$). Similar statistical results were obtained when increments in plasma insulin responses unadjusted for increments in plasma glucose concentrations were compared ($P = 0.013$ for first phase plasma insulin response; $P = 0.12$ for second phase plasma insulin response). DI 1st phase and DI 2nd phase were comparable in both groups consistent with both groups having similar glucose tolerance.

Using ANCOVA, adjustment for age, gender, 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 gender 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 three groups ($P > 0.2$), suggesting that the differences in insulin sensitivity were largely due to differences in obesity.

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 beta-cell function by a sustained increase in plasma free fatty acid 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 sub-groups with

a BMI <27 kg/m² (N=37 and N=21, respectively) and a BMI ≥ 27 kg/m² (N=37 and N=29, respectively), and compared the respective sub-groups using unpaired Student's t tests. In the sub-groups with a BMI <27 kg/m², first (21.7 ± 2.6 vs 23.8 ± 3.8 pM/mM, $P>0.6$) and second phase plasma insulin responses (29.5 [23.9–36.4] vs 33.8 [25.6–44.7] pM/mM, $P>0.4$) were not significantly different between IGT/FH+ and IGT/FH-. In contrast, in the sub-groups with a BMI ≥ 27 kg/m², 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 pM/mM, $P=0.018$); second phase plasma insulin responses were not statistically different (62.8 [52.4–75.3] vs 69.5 [56.6–85.1] pM/mM, $P>0.4$).

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 to normal glucose tolerant subjects, IGT subjects with a first degree T2DM relative had ~45% reduced first phase plasma insulin responses and ~30% reduced second phase plasma insulin responses whereas insulin sensitivity was only ~20% reduced. In contrast, IGT subjects without a first degree T2DM relative had ~40% reduced insulin sensitivity, but only ~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 25–30% lower first phase plasma insulin response ($P = 0.026$) but a 25–30% greater insulin sensitivity ($P = 0.027$). 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 due to a greater reduction in the ability of insulin secretion to compensate for insulin resistance. This may not only have implications regarding strategies for the prevention of T2DM but also regarding its risk, since progression of IGT to T2DM was linked to a greater defect in 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 beta-cell dysfunction but no insulin resistance independently of differences in obesity, estimated by BMI and waist-to-hip ratio. Similarly, we found that the greater insulin sensitivity in the IGT/FH+ group compared to 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 that 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 waist-to-hip ratio, we would not have found significant differences in insulin sensitivity between the control and IGT groups and the IGT/FH+ and the IGT/FH- group since insulin sensitivity was no longer significantly different when adjusted for obesity using analysis of covariance.

Recently, Kashyap et al. [15] demonstrated that a sustained increase in plasma free fatty acid 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. [22,23] and Paolisso et al. [22,23] have shown that a reduction in plasma FFA levels with the antilipolytic agent acipimox for two to seven days increased first phase plasma insulin responses in non-diabetic individuals having a first degree T2DM relative. In sub-analyses of our data, we therefore tested the hypothesis that obesity affects the genetic influence on beta-cell function in IGT by stratification of the IGT groups into subgroups using a BMI of 27 kg/m² 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 ~30% lower in IGT/FH+ with a BMI $\geq$ 27 kg/m² (P=0.018) but similar in IGT/FH- with a BMI <27 kg/m² compared to 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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Figure 1. Plasma concentrations of glucose and insulin during the hyperglycemic clamp in IGT subjects with (IGT/FH+) and without (IGT/FH-) a first degree T2DM relative, and subjects with normal glucose tolerance (NGT).

Table 1
Demographic and Anthropometric Characteristics of the Study Population and Results of the Oral Glucose Tolerance Tests

	P-value					
	IGT/FH+ ¹	IGT/FH- ²	Controls ³	1 vs 2	1 vs 3	2 vs 3
Age (years)	48.7 ± 1.4	50.4 ± 1.6	41.0 ± 1.0	>0.4	<0.001	<0.001
Gender (m/f)	26/48	25/25	36/97	=0.10	>0.2	<0.005
BMI (kg/m ²)	27.7 [26.5–29.0]	28.9 [27.7–30.1]	25.7 [25.1–26.3]	=0.17	<0.001	<0.001
Waist-to-hip Ratio	0.86 ± 0.01	0.90 ± 0.01	0.82 ± 0.01	<0.007	<0.001	<0.001
Fasting Plasma Glucose (mmol/l)	5.55 ± 0.06	5.60 ± 0.08	4.88 ± 0.03	>0.5	<0.001	<0.001
2-hour Plasma Glucose (mmol/l)	8.96 ± 0.10	9.02 ± 0.14	5.72 ± 0.08	>0.7	<0.001	<0.001
AUC Plasma Glucose (mmol/l · h)	7.59 ± 0.23	7.15 ± 0.24	3.32 ± 0.16	>0.2	<0.001	<0.001

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

Table 2

Results from the Hyperglycemic Clamp Test

	P-value					
	IGT/FH+ ¹	IGT/FH- ²	Controls ³	1 vs 2	1 vs 3	2 vs 3
1 st Phase (pM/mM) Insulin Secretion	26.3 ± 2.2	36.8 ± 4.1	47.2 ± 2.3	=0.026	<0.001	=0.016
2 nd Phase (pM/mM) Insulin Secretion	43.0 [36.5–50.8]	51.3 [42.5–62.0]	60.0 [53.8–66.8]	=0.148	<0.001	=0.157
Insulin Sensitivity Index ($\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}\cdot\text{pM}^{-1}$)	0.114 [0.097–0.133]	0.089 [0.075–0.105]	0.142 [0.129–0.157]	=0.027	=0.011	<0.001
Disposition Index, 1 st Phase ($\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}\cdot\text{mM}^{-1}$)	2.35 [2.01–2.75]	2.35 [1.95–2.84]	5.67 [5.05–6.37]	>0.9	<0.001	<0.001
Disposition Index, 2 nd Phase ($\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}\cdot\text{mM}^{-1}$)	4.89 [4.45–5.38]	4.56 [4.02–5.16]	8.53 [7.96–9.14]	>0.3	<0.001	<0.001

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

Table 3
Results from the Hyperglycemic Clamp Test adjusted for Age, Gender, BMI, and WHR using ANCOVA

	P-value			
	IGT/FH+ ¹	IGT/FH- ²	Controls ³	1 vs 2 1 vs 3 2 vs 3
1 st Phase Insulin Secretion (pM/mM)	25.8 ± 2.8	34.7 ± 3.6	48.2 ± 2.2	=0.047 <0.001 <0.002
2 nd Phase Insulin Secretion (pM/mM)	43.5 [37.2–50.7]	52.2 [43.3–63.1]	59.3 [52.7–66.7]	>0.5 <0.001 <0.001
Insulin Sensitivity Index ($\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}\cdot\text{pM}^{-1}$)	0.1114 [0.099–0.132]	0.090 [0.075–0.106]	0.141 [0.127–0.157]	- - *
Disposition Index, 1 st Phase ($\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}\cdot\text{mM}^{-1}$)	2.49 [2.14–2.90]	2.74 [2.26–3.32]	5.18 [4.61–5.82]	>0.4 <0.001 <0.001
Disposition Index, 2 nd Phase ($\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}\cdot\text{mM}^{-1}$)	4.97 [4.52–5.46]	4.68 [4.16–5.26]	8.38 [7.80–8.99]	>0.5 <0.001 <0.001

* F-test not significant.
Data of first phase insulin secretion are means ± SE. Other data are geometric means (95% confidence interval).