

# Insulin Secretion and Insulin Sensitivity Pattern Is Different in Isolated Impaired Glucose Tolerance and Impaired Fasting Glucose

## The Risk Factor in Impaired Glucose Tolerance for Atherosclerosis and Diabetes Study

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**OBJECTIVE** — Isolated impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are two risk categories for type 2 diabetes. This study compared both categories with respect to the degree of insulin secretion abnormalities and insulin resistance.

**RESEARCH DESIGN AND METHODS** — This is a crossover comparison of a population at high risk for type 2 diabetes. The subjects were recruited from the Risk Factor in Impaired Glucose Tolerance for Atherosclerosis and Diabetes (RIAD) study. They underwent a 75-g oral glucose tolerance test, with measurement of specific insulin, C-peptide, proinsulin, and free fatty acids at baseline and every 30 min after load for 2 h. Factor analysis was performed to evaluate the importance of insulin resistance and secretion abnormalities in both categories.

**RESULTS** — All categories of prediabetic hyperglycemia had a higher cardiovascular risk factor level when adjusted for sex, age, and BMI compared to control subjects with normal glucose tolerance. Subjects with isolated IFG were more insulin resistant than those with IGT. By contrast, subjects with isolated IGT exhibited a more severe deficit in early- and late-phase insulin secretion versus IFG subjects. As shown with factor analysis, in IFG the insulin resistance factor explained 28.4% of the variance, whereas in IGT the insulin secretion factor was dominant, explaining 31.1% of the total variance.

**CONCLUSIONS** — Our cross-sectional data from the RIAD study demonstrate that isolated IFG and isolated IGT are different with respect to the degree of insulin resistance and anomalies in insulin secretion, and that subjects with IGT exhibit a deficit in the early and late phases of insulin secretion. This finding may be important for a differential approach in primary prevention of type 2 diabetes.

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**Abbreviations:** AUC, area under the curve; CGI, combined glucose intolerance; CV, coefficient of variation; FFA, free fatty acid; FPG, fasting plasma glucose; HOMA, homeostasis model assessment; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; inc AUC, incremental AUC; IR-HOMA, HOMA insulin resistance index; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose; RIAD study, Risk Factor in Impaired Glucose Tolerance for Atherosclerosis and Diabetes study; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Impaired glucose tolerance (IGT), as defined by the World Health Organization (WHO) (1), is an established risk category for diabetes (2,3). Furthermore, IGT is associated with an increase in cardiovascular-related mortality and all-cause mortality (4). Impaired fasting glucose (IFG) is also a risk category for diabetes, but its relationship to atherosclerosis is less clear (5,6). There is now evidence that isolated IFG and isolated IGT may represent different populations with more or less overlapping subclinical characteristics and pathophysiology. Combined glucose intolerance (CGI), on the other hand, seems to represent a more advanced stage of prediabetes that bears a distinctly higher risk of conversion to diabetes and other comorbid illnesses (7,8). Recently published data from the Botnia Study (9) suggest that insulin resistance as measured by homeostasis model assessment (HOMA) is more increased in those with isolated IFG than in those with IGT. By contrast, Weyer et al. (10) found in Pima Indians that subjects with isolated IFG had more severe defects in acute insulin response than those with isolated IGT. In a study by Davies et al. (11), the fasting hyperglycemia group had a lower insulin secretion, whereas the IGT group had a higher 2-h insulin concentration. In the Botnia study, however, there was a significantly lower early insulin response in the IGT versus the IFG group (9). This study did not consider insulin fractions and late-phase insulin secretion as well as the impact of the subjects' sex. Differences in insulin sensitivity and secretion may be of importance for planning an intervention program. With the outcome of the STOP-NIDDM study using acarbose (12) and the Diabetes Prevention Program using metformin (13), a differential preventive strategy may be considered for

subtypes of preclinical abnormalities in glucose homeostasis. The Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes (RIAD) study is a prospective trial in middle-aged subjects to determine the risk for diabetes (14). This report analyzes the following questions: 1) Is there a difference in baseline characteristics and associated risk factors between isolated IFG and isolated IGT? 2) Are IFG and IGT different in insulin resistance and insulin fractions in the fasting state? and 3) Are they different in insulin response after a 75-g oral glucose load?

## RESEARCH DESIGN AND METHODS

### Study design

In this survey, subjects were ages 40–70 years and had a family history of type 2 diabetes, obesity, and/or dyslipoproteinemia. Details of the study design and recruitment have been reported elsewhere (15). Subjects were excluded from the study if they were known to have diabetes or were taking any medication that affects glucose tolerance or for infections, liver or kidney diseases, or thyroid function disorders. In the present study, a total of 664 subjects without diabetes were analyzed.

### Glucose tolerance

After subjects fasted overnight, they were administered an oral glucose tolerance test (OGTT) with 75 g glucose. Blood samples were collected before the test and every 30 min for a period of 2 h. Subjects were classified into categories of glucose tolerance according to the 1999 WHO diagnostic criteria. Isolated IFG was defined as having a fasting plasma glucose (FPG) level  $\geq 6.1$  to  $< 7.0$  mmol/l and a 2-h postchallenge glucose level  $< 7.8$  mmol/l. Isolated IGT was defined by an FPG level  $< 6.1$  mmol/l and a 2-h during OGTT glucose level  $\geq 7.8$  and  $< 11.1$  mmol/l. Subjects with FPG levels  $\geq 6.1$  and  $< 7.0$  mmol/l and 2-h during OGTT glucose level  $\geq 7.8$  and  $< 11.1$  mmol/l at 2 h after glucose load were considered as exhibiting CGI.

### Laboratory data

Serum was used for analysis of proinsulin, insulin, and C-peptide levels. Plasma glucose was measured in fresh material by the hexokinase method (interassay coefficient of variation [CV] 1.5%). HbA<sub>1c</sub> was examined by high-performance liquid

chromatography on a Diamat analyzer (BIORad Laboratories, Munich, Germany). HDL cholesterol was determined after precipitation with dextran sulfate on a Ciba Corning Express Plus analyzer (Ciba Corning Diagnostics, Fernwald, Germany). Triglycerides and total cholesterol were measured enzymatically. Free fatty acids (FFAs) were analyzed by enzyme colorimetric assay with a Boehringer Mannheim test kit. Proinsulin was measured by highly specific enzyme immunoassay (DGR Instruments, Marburg, Germany). The monoclonal antibody used in this assay recognizes a proinsulin specific epitope. It showed a cross-reactivity to a proinsulin 32–33 split  $< 1.5\%$  and none with human insulin and C-peptide (interassay CV 10–16%). Specific insulin and C-peptide were also determined by enzyme immunoassay (Medgenix Diagnostics, Fleurus, Belgium). Specific insulin (interassay CV 7.6%) showed no cross-reactivity to human proinsulin. The cross-reactivity of C-peptide assay to human proinsulin was 12.5% (interassay CV 11%).

### Statistics and calculations

Data evaluation was conducted using the SPSS 10.0 program (SPSS, Chicago, IL). Data are expressed as means  $\pm$  SD. Triglycerides and specific insulin (0 and 120 min) are represented as median and interquartile range. Proinsulin and C-peptide values were log-transformed to improve skewness and kurtosis. The areas under the curve (AUCs) for plasma glucose, insulin, proinsulin, and FFAs during the OGTT were calculated using the trapezoidal rule. Furthermore, to evaluate the FPG-related insulin response after load, the AUCs for plasma glucose and insulin were corrected for the fasting value to obtain incremental AUC (inc AUC).

Significance was determined at  $P < 0.05$ . Analysis for linear trend was carried out by ANOVA. Differences between groups were tested with a *t* test for unrelated samples. Pearson's correlation coefficients were obtained to estimate linear correlations between variables. Linear multiple regressions were used to assess the independent effect of several variables on basal glucose and 2-h plasma glucose (PG) during OGTT. The inclusion method was used.

As indexes of early insulin secretion, we used the early (after 30 min) incremental insulin response during the

OGTT, and the ratio of insulin-to-plasma glucose levels increment during the first 30 min of the OGTT ( $\Delta\text{INS}/\Delta\text{PG}$  30) (16). For the late phase, we considered the insulin excursion between 30 and 120 min after glucose load. As indicators of insulin resistance, we used the fasting specific insulin concentration and the HOMA insulin resistance index (IR-HOMA) (17).

Factor analysis was used to investigate relationships among several correlated variables by summarizing. The analysis consisted of extraction of initial components by using the principal component analysis, rotation of components using the orthogonal varimax method, and interpretation of the calculated factors.

**RESULTS**— Of the 664 subjects, 367 (55.2%) had normal glucose tolerance (NGT), 90 (13.6%) had IFG, 101 (15.2%) had IGT, and 106 (16.0%) had CGI. There were no differences in age between the IFG and IGT groups. There was, however, a striking sex difference between these categories. IFG was more prevalent in men (sex ratio 1.4) and IGT was more prevalent in women (sex ratio 1.7). In general, subjects with hyperglycemia were older than those with NGT ( $55.9 \pm 7.8$  vs.  $53.7 \pm 8.1$  years;  $P < 0.05$ ).

Because of strong differences in sex distribution in the different categories of hyperglycemia, we considered the risk factor profile separately for men and women. In men (Table 1), IFG, IGT, and CGI were associated with a higher level of established risk factors compared to NGT. The increase in HbA<sub>1c</sub> was only significant for IFG and CGI. Waist-to-hip ratios in the IFG and IGT groups were equal in both prediabetic categories. However, the FFA level was significantly higher in IGT than IFG.

In women (Table 2), the same tendencies could be observed: subjects with IFG, IGT, and CGI were more obese, exhibited higher levels of triglycerides, had lower HDL cholesterol, and displayed a nonsignificant increase in blood pressure. The only significant difference between women in the IFG and IGT groups was again a higher level of FFAs in the latter.

Insulin resistance as calculated by HOMA (Fig. 1) was significantly increased in all subgroups of hyperglycemia versus NGT subjects. Isolated IFG and CGI exhibited a significantly higher level of insulin resistance than IGT. Men in general exhibit a higher level of insulin

**Table 1—Risk factor profile by categories of glucose tolerance in men**

|                                 | NGT         | IFG          | IGT           | CGI           |
|---------------------------------|-------------|--------------|---------------|---------------|
| BMI (kg/m <sup>2</sup> )        | 26.0 ± 2.8  | 27.9 ± 3.9†  | 28.0 ± 4.3†   | 28.0 ± 3.3†   |
| Waist-to-hip ratio              | 0.95 ± 0.05 | 0.97 ± 0.05† | 0.97 ± 0.07†  | 0.98 ± 0.06†  |
| HbA <sub>1c</sub> (%)           | 5.47 ± 0.41 | 5.73 ± 0.46† | 5.60 ± 0.34   | 5.86 ± 0.50†‡ |
| Triglycerides (mmol/l)*         | 1.67 (1.07) | 2.24 (1.75)  | 2.49 (1.59)   | 2.86 (2.15)†  |
| Total cholesterol (mmol/l)      | 5.7 ± 1.0   | 6.0 ± 1.2    | 5.6 ± 1.2     | 5.9 ± 1.1     |
| HDL cholesterol (mmol/l)        | 1.28 ± 0.35 | 1.30 ± 0.28  | 1.20 ± 0.32   | 1.17 ± 0.30†§ |
| Free fatty acids (pmol/l)       | 0.36 ± 0.16 | 0.37 ± 0.17  | 0.47 ± 0.18†§ | 0.52 ± 0.23†§ |
| Systolic blood pressure (mmHg)  | 133 ± 18    | 138 ± 20     | 138 ± 22      | 140 ± 14†     |
| Diastolic blood pressure (mmHg) | 83 ± 10     | 86 ± 10      | 85 ± 9        | 87 ± 9†       |

Data are means ± SD, unless otherwise noted. \*Median (interquartile range) Kruskal-Wallis *H* test *P* < 0.0001; †ANOVA *P* < 0.05 vs. NGT; ‡ANOVA *P* < 0.001 vs. IGT; §ANOVA *P* < 0.05 vs. IFG.

resistance than do women independent of their category of glucose tolerance. Women and men with IFG and CGI had significantly higher levels of IR-HOMA than those with NGT. IFG women, but not IFG men, had a significantly enhanced insulin resistance versus their IGT counterparts.

Insulin fractions and insulin response to glucose load by category of glucose tolerance are shown in Table 3. Because insulin levels and postload excursions may be influenced by sex, age, and BMI, we performed an adjustment for these three variables. Fasting and 2-h postchallenge insulin fractions were increased in all categories of hyperglycemia. In general, 2-h postchallenge levels exhibited a tendency for higher levels in IGT than in IFG subjects. This reached significance for 2-h postchallenge C-peptide. The highest levels of proinsulin were observed in CGI (significant versus IGT).

The early insulin responses as measured by the increment after 30 min seemed to be similar in all categories of glucose tolerance. The ΔINS/ΔPG30, however, revealed a significant deficit in early insulin response in all three prediabetic categories versus the NGT group. CGI subjects exhibited a significantly lower response than IFG subjects, whereas the lower response in isolated IGT subjects did not reach statistical significance versus IFG subjects. Regarding the AUC of insulin, a significant hypersecretion seemed to appear in all subgroups with hyperglycemia after glucose load, which was significantly more expressed in subjects with CGI versus IFG. This was because of a significant increase in the second-phase insulin secretion (30–120 min postload). The hypersecretion, how-

ever, was no longer valid when the AUC for insulin was related to the AUC for plasma glucose. The incremental AUC in IGT and CGI subjects was even significantly lower (*P* < 0.05) than in IFG subjects. The AUC for FFAs was significantly increased only in the IGT and CGI groups. In addition, the IGT group had higher levels of FFAs than the IFG group after glucose load.

As shown in Fig. 2, the IFG, IGT, and CGI subjects were different in their glucose and insulin excursion response to the 75-g glucose load as compared to NGT subjects. The postchallenge glucose and insulin peaks were later and higher in IGT and CGI subjects than in NGT and IFG subjects, with a slower decrement seen in the prior. Proinsulin was significantly higher at baseline in IFG versus NGT subjects. At 2-h after glucose challenge, however, levels of proinsulin were significantly elevated in the CGI versus NGT, IFG, and IGT groups.

Factor analysis was performed for the IGT and IFG subjects (Fig. 3). For IFG

subjects, factor 1 (the “insulin resistance factor”) was dominant, with IR-HOMA as the strongest component. This factor explained 28.4% of total variance. Factor 2 (the “metabolic factor”), with glucose increment, glucose peak, and FFAs, explained only 10.9% of the variation. For IGT subjects, factor 1 (the “insulin secretion factor”) revealed early insulin secretion and 2-h insulin as dominating factors, explaining 31.1% of the variation, whereas factor 2 for IGT subjects (the “insulin resistance factor”) explained only 9.4% of the variation.

**CONCLUSIONS**— Our data in a high-risk population for diabetes provide further evidence that isolated IFG and isolated IGT are different with respect to their pathophysiological basis. Despite the fact that subjects in both categories did not differ with regard to age, BMI, HbA<sub>1c</sub>, blood lipids, smoking habits, and blood pressure, they exhibited significant differences in insulin sensitivity, insulin response to a 75-g standard OGTT, and FFA levels.

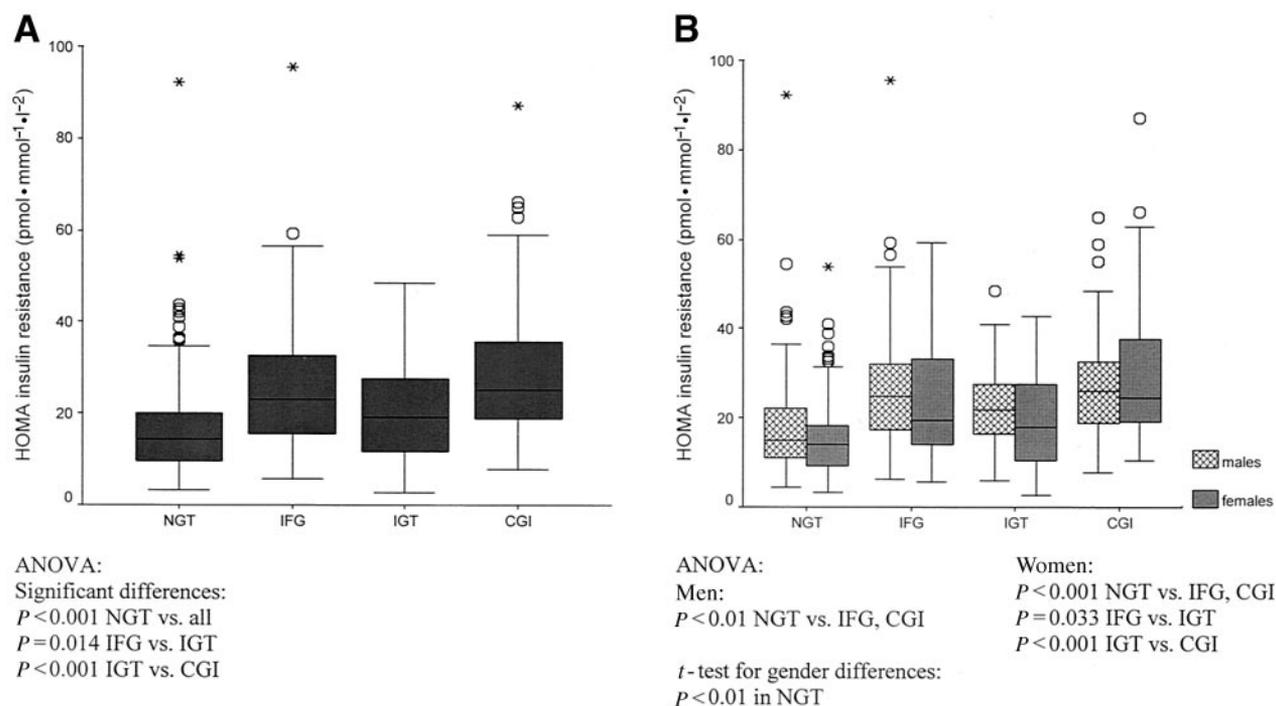
As in other studies (2,3,18), IFG was more prevalent among men and IGT was more prevalent among women. According to published cross-sectional data (3,18,19), all prediabetic categories have a somewhat higher level of cardiovascular risk factors, except for total cholesterol, than do NGT subjects. There are, however, no significant differences in major risk factors between IFG and IGT subjects for either sex. As in the Paris Prospective Study (20), FFA levels were significantly higher in IGT than in IFG subjects for both sexes in our study.

Fasting insulin, C-peptide, and proinsulin levels were significantly increased

**Table 2—Risk factor profile by categories of glucose tolerance in women**

|                                 | NGT         | IFG           | IGT           | CGI           |
|---------------------------------|-------------|---------------|---------------|---------------|
| BMI (kg/m <sup>2</sup> )        | 25.9 ± 4.6  | 27.4 ± 4.4    | 27.8 ± 5.9†   | 29.0 ± 4.6†   |
| Waist-to-hip ratio              | 0.81 ± 0.09 | 0.84 ± 0.07   | 0.83 ± 0.06   | 0.87 ± 0.06†‡ |
| HbA <sub>1c</sub> (%)           | 5.45 ± 0.41 | 5.65 ± 0.53†  | 5.52 ± 0.48   | 5.79 ± 0.62†‡ |
| Triglycerides (mmol/l)*         | 1.19 (0.56) | 1.43 (1.28)   | 1.54 (0.77)   | 1.73 (1.48)   |
| Total cholesterol (mmol/l)      | 5.8 ± 1.1   | 5.7 ± 1.0     | 6.0 ± 1.1     | 5.9 ± 1.0     |
| HDL cholesterol (mmol/l)        | 1.71 ± 0.43 | 1.52 ± 0.348† | 1.56 ± 0.39†  | 1.49 ± 0.44†  |
| FFAs (pmol/l)                   | 0.45 ± 0.21 | 0.51 ± 0.23   | 0.60 ± 0.24†§ | 0.56 ± 0.19†  |
| Systolic blood pressure (mmHg)  | 132 ± 18    | 136 ± 20      | 136 ± 19      | 137 ± 18      |
| Diastolic blood pressure (mmHg) | 83 ± 10     | 83 ± 10       | 84 ± 9        | 84 ± 9        |

Data are means ± SD, unless otherwise noted. \*Median (interquartile range), Kruskal-Wallis *H* test *P* < 0.0001; †ANOVA *P* < 0.05 vs. NGT; ‡ANOVA *P* < 0.001 vs. IGT; §ANOVA *P* < 0.05 vs. IFG.



**Figure 1**—Box plots of insulin resistance by categories of glucose tolerance total (A) and by sex (B) adjusted by age and BMI. ■, men; ■, women; ○, outliers; black line in box, median; \*extreme value.

in all three categories of hyperglycemia in our study. Tripathy et al. (9) and Davies et al. (11) have described increased fasting insulin fractions for IGT and fasting hyperglycemia. This could be explained by the higher level of insulin resistance in the hyperglycemia categories. It is well documented that increases in insulin resis-

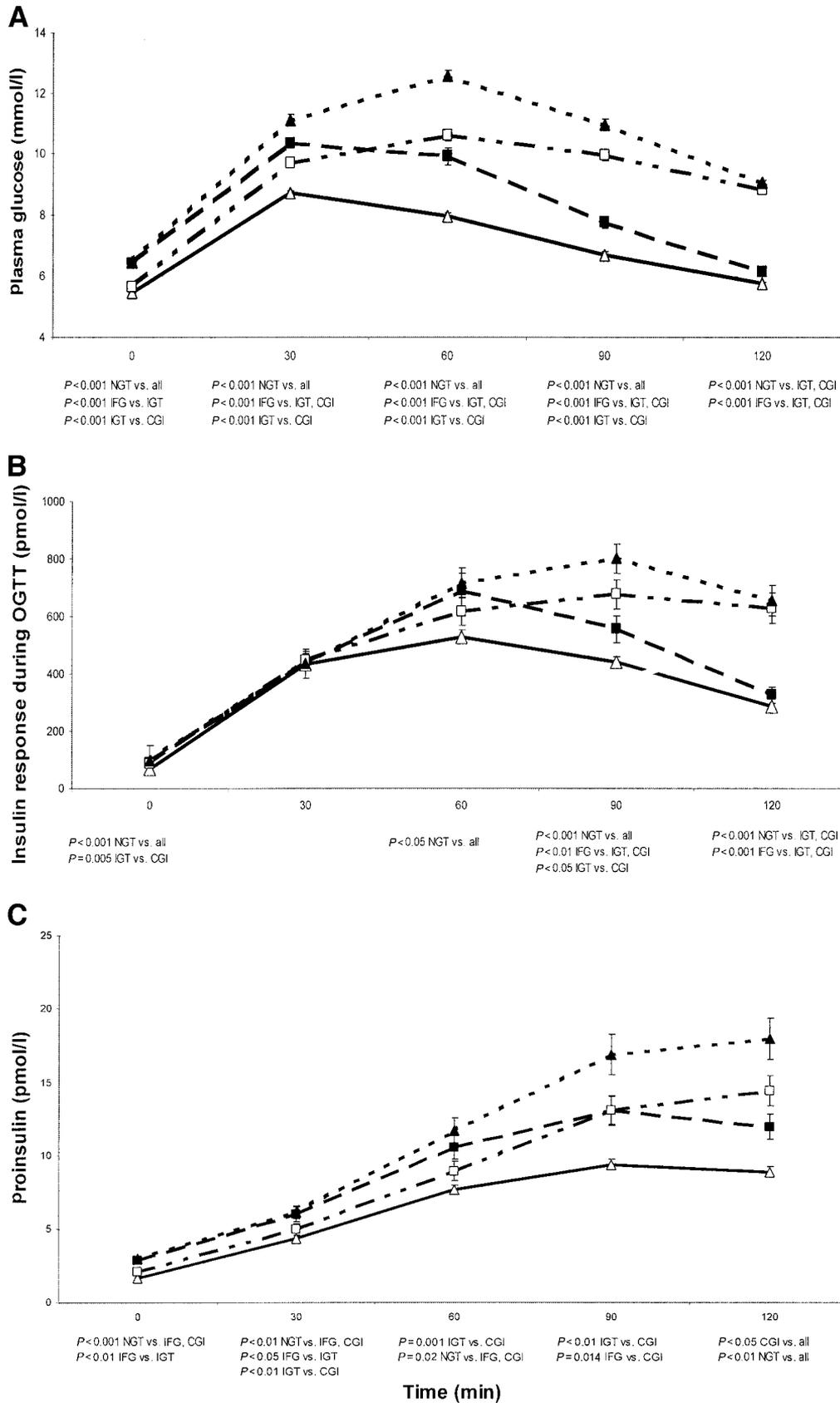
tance begin long before diabetes is diagnosed (10,21–23). Interestingly, our data showed a significantly higher degree of insulin resistance in isolated IFG versus IGT subjects when calculated with the IR-HOMA. The difference in insulin resistance between isolated IFG and IGT subjects based on this calculation may un-

derestimate the degree of insulin resistance, because isolated IGT per definition has a low fasting plasma glucose level that contributes to a low IR-HOMA value. Therefore, our finding needs to be further confirmed by clamp investigations. Insulin resistance was also more expressed in CGI compared to IGT

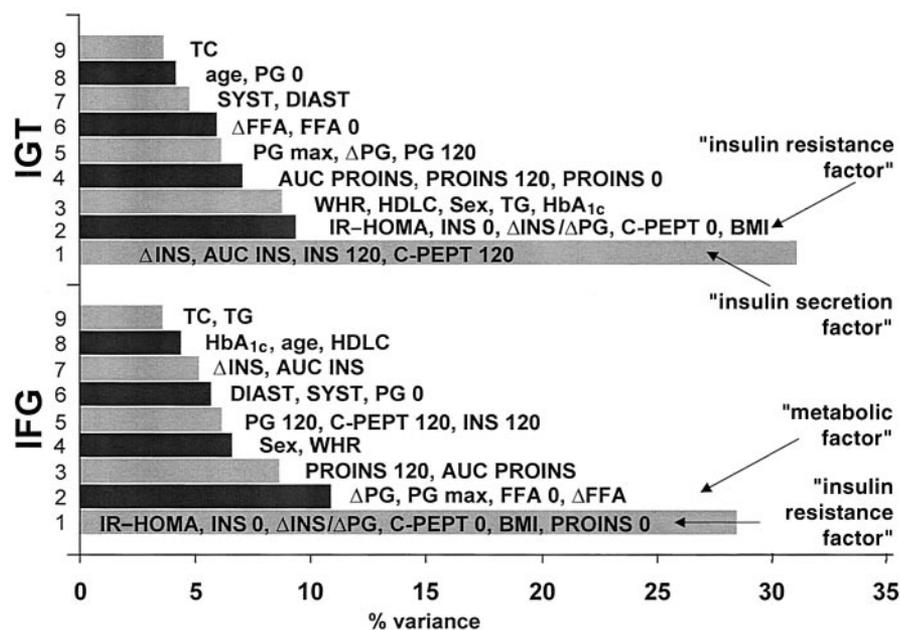
**Table 3**—Insulin fractions and insulin secretion related to types of hyperglycemia adjusted by sex, age, and BMI

|  | NGT             | IFG              | IGT              | CGI               |
|--|-----------------|------------------|------------------|-------------------|
| Insulin (pmol/l)*                                      |                 |                  |                  |                   |
| Fasting  | 59.0 (40.0)     | 79.0 (56.5)      | 80.0 (63.5)      | 87.0 (53.8)       |
| 2-h OGTT   | 230 (174)       | 272 (205)        | 478 (388)        | 550 (387)         |
| C-peptide (pmol/l)                                     |                 |                  |                  |                   |
| Fasting  | 1,070 ± 443     | 1,380 ± 512†     | 1,305 ± 628†     | 1,416 ± 486†      |
| 2-h OGTT (pmol/l)                                      | 3,521 ± 1,310   | 4,070 ± 1,413†   | 5,063 ± 1,316†&  | 5,192 ± 1,423†&   |
| Proinsulin (pmol/l)*                                   |                 |                  |                  |                   |
| Fasting  | 1.45 (1.16)     | 2.1 (1.93)†      | 1.7 (1.82)       | 2.31 (2.40)†\$    |
| 2-h OGTT   | 8.87 (6.37)     | 12.02 (8.02)†    | 14.49 (10.39)†   | 17.97 (14.39)†&\$ |
| Inc insulin 30 min (pmol/l)**                          | 367 ± 268       | 354 ± 266        | 362 ± 288        | 337 ± 278         |
| ΔINS/PG30 ratio × 10 <sup>-8</sup>                     | 14.3 ± 19.2     | 11.1 ± 10.9§     | 9.1 ± 6.1§       | 9.0 ± 21.1§#      |
| AUC insulin during OGTT (pmol/l)                       | 46,893 ± 33,004 | 56,983 ± 37,687† | 63,602 ± 45,502† | 70,224 ± 41,735†& |
| AUC insulin 30–120 min during OGTT (pmol/l)            | 39,378 ± 29,241 | 48,963 ± 33,854† | 55,512 ± 40,583† | 62,203 ± 37,729†& |
| AUC insulin to AUC PG ratio × 10 <sup>-8</sup> **      | 53.1 ± 31.9     | 54.6 ± 32.5      | 55.2 ± 37.0      | 54.8 ± 31.1       |
| Inc AUC insulin to Inc AUC PG ratio × 10 <sup>-8</sup> | 21.9 ± 51.9     | 17.1 ± 30.1      | 12.2 ± 8.4§#     | 12.0 ± 7.4§#      |
| AUC free fatty acids during OGTT (pmol/l)              | 19.2 ± 8.2      | 22.3 ± 10.8      | 28.5 ± 11.3†&    | 34.3 ± 33.4†&\$   |

Data are means ± SD, unless otherwise noted. \*Median (interquartile range), Kruskal-Wallis  $H$  test  $P < 0.0001$ ; \*\*ANOVA  $P < 0.05$  for trend; †ANOVA  $P < 0.05$  vs. NGT; &ANOVA  $P < 0.05$  vs. IFG; \$ANOVA  $P < 0.05$  vs. IGT; §ANOVA with logarithmic value  $P < 0.001$  vs. NGT; ‡ANOVA with logarithmic value  $P < 0.05$  vs. IGT; #ANOVA with logarithmic value  $P < 0.05$  vs. IFG. Inc, incremental.



**Figure 2**—Plasma glucose (A), insulin (B), and proinsulin (C) excursion after a 75-g OGTT in different categories of glucose tolerance (means  $\pm$  SEM, tested by ANOVA).  $\Delta$ , NGT;  $\blacksquare$ , IFG;  $\square$ , IGT;  $\blacktriangle$ , CGI



**Figure 3**—Variance of factors in factor analysis by parameters of insulin secretion, sensitivity, and metabolism in isolated IFG and IGT. AUC INS, AUC during OGTT of insulin; AUC PROINS, AUC proinsulin during OGTT; C-PEPT 0, C-peptide basal; C-PEPT 120, C-peptide 2-h OGTT; DIAST, diastolic blood pressure; FFA 0 free fatty acids basal; Δ FFA, FFA 30–0 min; HDLC, HDL cholesterol; INS 0, insulin basal; INS 120, insulin 2-h OGTT; Δ INS, increment insulin 30–0 min; PG 0, plasma glucose basal; PG 120, plasma glucose 2-h OGTT; Δ PG, increment PG30–0 min; PG max, maximal plasma glucose value in OGTT; PROINS 0, proinsulin basal; PROINS 120, proinsulin 2-h OGTT; SYST, systolic blood pressure, TC, total cholesterol; TG, triglycerides; WHR, waist-to-hip ratio.

subjects. In accordance with our finding in the Botnia Study (9), IFG was associated with a higher level of insulin resistance than IGT. This latter study did not differentiate for sex, despite a strong discrepancy in sex distribution, similar to our findings. It is obvious that differences in the degree of insulin resistance are strongly affected by sex distribution. The difference in IR-HOMA by sex between IFG and IGT groups was significant only for women.

On the other side, a significant deficit in early insulin secretion was observed in all three risk categories for diabetes with regard to the  $\Delta$ INS/ $\Delta$ PG 30 ratio. The 30-min postchallenge insulin increment, however, was still at the same level as in NGT subjects. This illustrated that insulin concentrations alone without taking into account corresponding glucose values may be misleading with respect to insulin secretion capacity (9,23). CGI subjects had a significantly lower insulin secretion than those with IFG, whereas the distinctly lower response in IGT versus IFG subjects failed to reach significance. In the Botnia study (9), IGT was associated with a significantly lower early insulin secretion compared to IFG. That study did not adjust for age, sex, or BMI. Our data, after adjustment for these confounders, showed in principle the same tendency, with a lower early phase of insulin secretion in IGT versus IFG subjects. By contrast, investigations in Pima Indians have shown that, with regard to the acute insu-

lin response after intravenous glucose injection, IFG subjects have more severe defects than those with isolated IGT. The acute insulin response in this study was plotted as a function of the mean *M* value of insulin resistance for the different categories of glucose tolerance (23). The differences in insulin excursion pattern by categories of hyperglycemia were even more expressed in the second phase. Subjects with NGT and IFG reached their peak level for insulin after 60 min, and those with IGT, after 90 min. A long-lasting second phase with “hypersecretion” was observed in subjects with IGT and CGI. Accordingly, the proinsulin excursion curves were also clearly different between IFG and IGT subjects. In general, the late postchallenge insulin secretion pattern was more abnormal in IGT and CGI subjects than in IFG subjects. All three categories of hyperglycemia had a significantly higher AUC for insulin at 30–120 min. This all seems to support a more expressed hyperinsulinemia and hyperproinsulinemia in IGT in the late phase when compared to IFG. However, when we calculated the ratio of incremental AUC for insulin to incremental AUC PG, a significant deficit for the second phase of insulin secretion in IGT versus isolated IFG was found. Thus impaired insulin secretion can be seen early also in the second phase of insulin secretion in all categories of hyperglycemia, which is clearly more advanced in IGT and CGI than in IFG.

By extrapolation, all three prediabetic categories exhibited a significant increase in insulin resistance and a deficit in insulin secretion. This finding supports recently published data (21,22) that insulin resistance and deficit in the early insulin secretion phase starts in parallel long before diabetes is diagnosed. Subjects with isolated IFG and IGT, however, differed in three aspects: their insulin resistance and their early- and late-phase insulin secretion after glucose load. They also differed in their postload glucose and FFA profile. The differences in underlying pathophysiology were confirmed by factor analysis. The insulin resistance factor was more predictive of IFG, explaining 28.4% of variance, whereas the insulin secretion factor was more predictive of IGT, explaining 31.1% of total variance. The distinct differences in underlying pathophysiology between isolated IFG and IGT may have consequences for clinical outcome and the planning of primary prevention trials.

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