Changes in Insulin Sensitivity and Insulin Release in Relation to Glycemia and Glucose Tolerance in 6,414 Finnish Men
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OBJECTIVE—We evaluated insulin sensitivity and insulin secretion across the entire range of fasting (FPG) and 2-h plasma glucose (PG), and we investigated the differences in insulin sensitivity and insulin release in different glucose tolerance categories.

RESEARCH DESIGN AND METHODS—A total of 6,414 Finnish men (aged 57 ± 7 years, BMI 27.0 ± 3.9 kg/m²) from our ongoing population-based METSIM (Metabolic Syndrome in Men) study were included. Of these subjects, 2,168 had normal glucose tolerance, 2,859 isolated impaired fasting glucose (IFG), 217 isolated impaired glucose tolerance (IGT), 701 a combination of IFG and IGT, and 469 newly diagnosed type 2 diabetes.

RESULTS—The Matsuda index of insulin sensitivity decreased substantially within the normal range of FPG (−17%) and 2-h PG (−37%) and was approximately −65 and −53% in the diabetic range of FPG and 2-h PG, respectively, compared with the reference range (FPG and 2-h PG <5.0 mmol/l). Early-phase insulin release declined by only approximately −5% within the normal range of FPG and 2-h PG but decreased significantly in the diabetic range of FPG (by 32–70%) and 2-h PG (by 33–51%). Changes in insulin sensitivity and insulin secretion in relation to hyperglycemia were independent of obesity. The predominant feature of isolated IGT was impaired peripheral insulin sensitivity. Isolated IFG was characterized by impaired early and total insulin release.

CONCLUSIONS—Peripheral insulin sensitivity was already decreased substantially at low PG levels within the normoglycemic range, whereas impairment in insulin secretion was observed mainly in the diabetic range of FPG and 2-h PG. Obesity did not affect changes in insulin sensitivity or insulin secretion in relation to hyperglycemia. Diabetes 58:1212–1221, 2009

Type 2 diabetes is preceded by a long pre-diabetic state, characterized by mild elevation of fasting and/or postprandial glucose levels. This asymptomatic phase may last for years, and about one-third of these individuals finally develop type 2 diabetes (1). The pre-diabetic state, defined by an oral glucose tolerance test (OGTT), includes impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or their combination (2). Epidemiological studies have shown that IFG and IGT represent two distinct subgroups of abnormal glucose tolerance (1,3–5) that differ in their age and sex distribution (6,7) and associated cardiovascular risk (8). Therefore, IFG and IGT are likely to have different pathophysiologicals.

Impaired insulin secretion and impaired insulin action are the two main pathophysiological disturbances leading to abnormal glucose tolerance. Previous studies on the role of impaired insulin secretion and insulin resistance in the development of IFG and IGT have yielded contradictory results (4–23). Inconsistencies across the studies are explained by differences in study populations, study designs and methods to assess insulin resistance and insulin secretion, and most importantly by a small sample size. Categorization of glucose tolerance is based on arbitrary cutoff points of glucose levels, and therefore different subgroups cannot fully account for changes in β-cell function and insulin action with increasing glycaemia. Only a few studies have examined insulin secretion and/or insulin sensitivity as a function of glucose concentrations (13,24–28). These studies have been, however, relatively small, and most of them were conducted in non-Caucasian populations.

The aim of this study was to evaluate insulin sensitivity and insulin secretion across the entire range of fasting and 2-h plasma glucose (PG) from normal glucose tolerance (NGT) to type 2 diabetes to understand better the pathophysiology of the pre-diabetic state. Furthermore, we investigated the differences in insulin sensitivity and insulin release in different glucose tolerance subgroups. To address these questions, we collected a large sample of carefully phenotyped middle-aged Finnish men.

RESEARCH DESIGN AND METHODS
A total of 6,414 men from the ongoing population-based cross-sectional Metabolic Syndrome in Men (METSIM) study were included in the study. Subjects, aged from 45 to 70 years, were randomly selected from the population register of the town of Kuopio in eastern Finland (population 95,000). Every participant had a 1-day outpatient visit to the Clinical Research Unit at the University of Kuopio, including an interview on the history of previous diseases and current drug treatment and an evaluation of glucose tolerance and cardiovascular risk factors. Fasting blood samples were drawn after 12 h of fasting followed by an OGTT. The study was approved by the ethics committee of the University of Kuopio and Kuopio University Hospital, and it was in accordance with the Helsinki Declaration.

Clinical measurements. Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. BMI was calculated as weight (kg) divided by height (m) squared. Waist (at the midpoint between the lateral iliac crest and lowest rib) and hip circumference (at the level of the trochanter major) were measured to the nearest 0.5 cm. Body composition was determined by...
Spearman correlation coefficients between surrogate indexes of β-cell function and insulin release during the first phase (0–10 min) and second phase (10–60 min) and total (0–60 min) during an IVGTT

| β-Cell function indexes | Insulin release during an IVGTT |
|-------------------------|--------------------------------|
|                         | First phase | Second phase | Total |
| HOMA-β                  | 0.568      | 0.645       | 0.663 |
| Insulinogenic index     | 0.579      | 0.469       | 0.541 |
| InsAUC30/GluAUC30        | 0.666      | 0.707       | 0.743 |
| ΔInsAUC120/ΔGluAUC120    | 0.375      | 0.409       | 0.405 |
| InsAUC120/GluAUC120      | 0.648      | 0.750       | 0.775 |
| First-phase Stumvoll    | 0.651      | 0.663       | 0.702 |
| Second-phase Stumvoll   | 0.662      | 0.692       | 0.730 |
| Fasting insulin         | 0.548      | 0.747       | 0.735 |
| Insulin at 30 min of an OGTT | 0.615   | 0.691       | 0.715 |
| Insulin at 120 min of an OGTT | 0.429   | 0.673       | 0.645 |
| Insulin AUC during an OGTT | 0.558   | 0.770       | 0.776 |

P < 0.001 for all correlation coefficients. Indexes of β-cell function were calculated as described previously: HOMA-β (30), insulinogenic index (31), ΔInsAUC120/ΔGluAUC120 (25), InsAUC120/GluAUC120 (31), first phase Stumvoll (32), and second phase Stumvoll (32). InsAUC120/GluAUC120 = (insulin at 0 min + insulin at 30 min of an OGTT)/ (glucose at 0 min + glucose at 30 min of an OGTT).

### RESULTS

**Baseline characteristics.** The age of 6,414 men in this study was 57 ± 7 years, and their BMI was 27.0 ± 3.9 kg/m². Altogether, 2,168 subjects (34%) had NGT, 2,859 (45%) had isolated IFG, 217 (3%) had isolated IGT, 701 (11%) had a combination of IFG and IGT, and 409 (7%) had newly diagnosed type 2 diabetes. A total of 492 subjects with previously diagnosed diabetes were excluded from statistical analyses. As shown in Table 3, subjects with NGT and isolated IFG were significantly younger than subjects with isolated IGT, IFG + IGT, and newly diagnosed type 2 diabetes. Subjects with isolated IGT were significantly more obese than subjects with isolated IFG and newly diagnosed type 2 diabetes.
Insulin sensitivity according to fasting and 2-h PG concentration. We generated different categories of FPG and 2-h PG to investigate the relationship between the peripheral insulin sensitivity (Matsuda ISI) or markers of early-phase and total glucose-stimulated insulin secretion and glyceremia. Categories with FPG < 5.0 mmol/l and 2-h PG < 5.0 mmol/l were set as the reference categories. We observed a considerable decrease in age- and BMI-adjusted peripheral insulin sensitivity (−17%) within the normal range of FPG, compared with the reference category. Insulin sensitivity further decreased to −50% within the range of IFG and decreased to −67% in the diabetic range of FPG (Fig. 1A). A substantial decrease in insulin sensitivity (−37%) was also observed within the normal range of 2-h PG. Insulin sensitivity further decreased to −51% within the IGT range and to −57% within the diabetic range of 2-h PG (Fig. 1B). When changes in insulin sensitivity according to the levels of both FPG and 2-h PG were examined, the highest insulin sensitivity was observed in subjects with FPG < 5.0 mmol/l and 2-h PG < 5.0 mmol/l, and the lowest insulin sensitivity was seen in subjects in the diabetic range of FPG and 2-h PG (supplementary Fig. 1, available in an online appendix at http://diabetes.diabetesjournals.org/cgi/content/full/db08-1607/DC1).

Insulin release according to fasting and 2-h PG concentration. Age- and BMI-adjusted early-phase insulin release (InsAUC30/GluAUC30) decreased only slightly (−4%) within the normal range of FPG. It further decreased within the range of IFG and diabetes to −25 and −70%, respectively (Fig. 1C). The early-phase insulin release decreased by −6% within the normal range of 2-h PG, and further decreased to −23 and −50% within the range of IGT and diabetes, respectively (Fig. 1D). Age- and BMI-adjusted total insulin release (InsAUC120/GluAUC120) decreased to −13% within the range of IFG, and to −70% within the diabetic range of FPG (Fig. 1E). Total insulin release increased by 14% with higher 2-h PG up to 9.9 mmol/l, and then it decreased to −45% within the diabetic range of 2-h PG (Fig. 1F). The largest decreases in both early-phase (−32 to −50%) and total (−17 to −45%) insulin release were observed within the range of FPG from 7.0 to 7.9 mmol/l (Fig. 1C and E).

Disposition index. The early-phase DI30 and total DI120 decreased with higher FPG within the normal range by −21 and −18%, respectively. Within the IFG range, the reduction in DI30 and DI120 reached −63 and −57% (Fig. 2A). As a function of 2-h PG, DI30 and DI120 decreased to −41 and −30% in the normal range and further decreased to −60 and −48% in the IGT range (Fig. 2B).

Compensatory insulin secretion. Compensatory insulin secretion was not observed, despite a significant decrease in insulin sensitivity within the normal range of FPG, but, in contrast, the early-phase insulin release started to fall. However, compensatory total insulin secretion already started at low 2-h PG levels, and insulin release increased up to 10 mmol/l and then started to decrease (supplementary Fig. 2). A decrease in DI indexes was already substantial in the normal ranges of FPG and 2-h PG. Our findings remained essentially similar after adjustment for glucose level (analyses based on FPG were adjusted for 2-h PG, and analyses based on 2-h PG were adjusted for FPG) in addition to age and BMI.

Insulin sensitivity and insulin release according to glucose levels in nonobese and obese individuals. No significant interaction between BMI and glucose levels in determining insulin sensitivity was found. Obese subjects (BMI ≥ 27 kg/m²) within the reference categories of FPG and 2-h PG (< 5.0 mmol/l) had reduced insulin sensitivity by −45 and −41% compared with nonobese subjects (BMI < 27 kg/m²). The decrease in insulin sensitivity with higher FPG and 2-h PG was similar in both nonobese and obese subgroups: −17% (nonobese subjects) and −13% (obese subjects) within the normal range of FPG and −37 and −36%, respectively, within the normal range of 2-h PG (Fig. 3A and B). Obese subjects within the reference categories of FPG and 2-h PG had increased early-phase (+70 and +54%) and total insulin release (+68 and +46%) compared with nonobese subjects. However, changes in both early-phase and total insulin release with higher FPG or 2-h PG were comparable in nonobese and obese subjects (Fig. 3). The interaction between glucose levels and BMI (cutoff point of 27 kg/m²) in determining insulin release was not significant, except for the interaction between 2-h PG and BMI in determining DI120 (P = 0.001).

Data are means ± SD or n (%). P values for overall comparison between five categories of glucose tolerance are shown (ANOVA for continuous variables, χ2 test for categorical variables). Bonferroni post hoc tests (continuous variables): all pairwise comparisons between categories of glucose tolerance were significant at P < 0.05, except for those marked as follows: *P < 0.05 vs. isolated IGT; †P < 0.05 vs. IFG + IGT; ‡P < 0.05 vs. isolated IFG; §P > 0.05 vs. NGT.

| Table 3 | Clinical and anthropometric characteristics of study participants according to glucose tolerance status |
|--------|--------------------------------------------------------------------------------------------------|
|        | n  | NGT | Isolated IFG | Isolated IGT | IFG + IGT | Newly diagnosed diabetes | P    | Total |
| Age (years) | 6,414 | 57.5 ± 6.7 | 56.7 ± 6.8 | 60.3 ± 6.9 | 59.2 ± 6.8* | 59.6 ± 6.4† | 6 × 10−31 | 57.7 ± 6.8 |
| BMI (kg/m²) | 6,410 | 25.8 ± 3.4 | 27.0 ± 3.6 | 26.9 ± 3.7‡ | 28.9 ± 4.4 | 29.7 ± 4.9 | 8 × 10−131 | 27.0 ± 3.9 |
| Weight (kg) | 6,411 | 79.8 ± 11.7 | 83.9 ± 12.7 | 82.4 ± 13.4§§ | 88.7 ± 14.8 | 91.0 ± 15.6 | 3 × 10−93 | 83.5 ± 13.3 |
| Waist circumference (cm) | 6,410 | 94.6 ± 9.6 | 97.9 ± 10.4 | 98.7 ± 10.1†† | 103.5 ± 11.5 | 105.7 ± 12.0 | 2 × 10−140 | 98.0 ± 10.9 |
| Hip circumference (cm) | 6,409 | 99.4 ± 6.2 | 101.1 ± 6.4 | 100.6 ± 6.7‡‡ | 103.4 ± 7.9 | 104.5 ± 8.1* | 3 × 10−73 | 101.1 ± 6.8 |
| Waist-to-hip ratio | 6,408 | 6.8 ± 0.6 | 6.9 ± 0.6 | 6.8 ± 0.6 | 6.8 ± 0.6 | 6.8 ± 0.6 | 1 × 10−108 | 6.8 ± 0.6 |
| Fat mass (%) | 6,408 | 22.5 ± 6.3 | 23.4 ± 6.0 | 26.2 ± 6.8 | 27.2 ± 6.7* | 27.7 ± 6.1† | 3 × 10−108 | 23.9 ± 6.5 |
| BMI ≥ 27 kg/m² (median) | 6,410 | 68.8 (31) | 1,276 (45) | 110 (51) | 452 (65) | 324 (69) | 1 × 10−84 | 2,831 (44) |
| Positive family history of diabetes | 6,412 | 889 (41) | 1,340 (47) | 104 (48) | 348 (50) | 254 (54) | 5 × 10−8 | 2,935 (46) |
Insulin sensitivity and insulin release in categories of glucose tolerance. Age- and BMI-adjusted peripheral insulin sensitivity (Matsuda ISI) was significantly decreased by 26% in isolated IFG, by 30% in isolated IGT, by 42% in IFG/IGT, and by 46% in newly diagnosed type 2 diabetes, compared with NGT (Fig. 4A). Matsuda ISI was significantly lower in individuals with isolated IGT than in individuals with isolated IFG ($P = 0.0016$). A significantly greater decrease in isolated IFG than in isolated IGT ($8\%$ vs. $0\%$, $P = 0.0028$) was found when insulin sensitivity was assessed with $1$/HOMA-IR. $1$/HOMA-IR was reduced by 39% in the IFG + IGT group and by 45% in newly diagnosed type 2 diabetic subjects (Fig. 4B). Categories of glucose tolerance status differed significantly also with respect to other indexes of insulin sensitivity (Table 4). Compared with NGT, the age- and BMI-adjusted early-phase insulin release ($\text{InsAUC}_{30}/\text{GluAUC}_{30}$) ($C$ and $D$), and total insulin release during the OGTT ($\text{InsAUC}_{120}/\text{GluAUC}_{120}$) ($E$ and $F$) across the categories of FPG and 2-h PG. Bars display the value of insulin sensitivity or insulin release relative to the reference category (FPG < 5.0 mmol/l, 2-h PG < 5.0 mmol/l). Calculations were based on geometric means, adjusted for age and BMI with the general linear model. Cutoff values for different categories of FPG were (in mg/dl): 90.1 (5.0 mmol/l), 99.1 (5.5 mmol/l), 108.1 (6.0 mmol/l), 117.1 (6.5 mmol/l), 126.1 (7.0 mmol/l), 135.1 (7.5 mmol/l), 144.1 (8.0 mmol/l), 153.2 (8.5 mmol/l), and 162.2 (9.0 mmol/l). Cutoff values for different categories of 2-h PG were (in mg/dl): 90.1 (5.0 mmol/l), 108.1 (6.0 mmol/l), 126.1 (7.0 mmol/l), 144.1 (8.0 mmol/l), 162.2 (9.0 mmol/l), 180.2 (10.0 mmol/l), 198.2 (11.0 mmol/l), 216.2 (12.0 mmol/l), and 234.2 (13.0 mmol/l).

**FIG. 1.** Insulin sensitivity (Matsuda ISI) ($A$ and $B$), early-phase insulin release ($\text{InsAUC}_{30}/\text{GluAUC}_{30}$) ($C$ and $D$), and total insulin release during the OGTT ($\text{InsAUC}_{120}/\text{GluAUC}_{120}$) ($E$ and $F$) across the categories of FPG and 2-h PG. Bars display the value of insulin sensitivity or insulin release relative to the reference category (FPG < 5.0 mmol/l, 2-h PG < 5.0 mmol/l). Calculations were based on geometric means, adjusted for age and BMI with the general linear model. Cutoff values for different categories of FPG were (in mg/dl): 90.1 (5.0 mmol/l), 99.1 (5.5 mmol/l), 108.1 (6.0 mmol/l), 117.1 (6.5 mmol/l), 126.1 (7.0 mmol/l), 135.1 (7.5 mmol/l), 144.1 (8.0 mmol/l), 153.2 (8.5 mmol/l), and 162.2 (9.0 mmol/l). Cutoff values for different categories of 2-h PG were (in mg/dl): 90.1 (5.0 mmol/l), 108.1 (6.0 mmol/l), 126.1 (7.0 mmol/l), 144.1 (8.0 mmol/l), 162.2 (9.0 mmol/l), 180.2 (10.0 mmol/l), 198.2 (11.0 mmol/l), 216.2 (12.0 mmol/l), and 234.2 (13.0 mmol/l).
insulin release than individuals with isolated IGT (−6 vs. +16%, \( P = 0.001 \)). The HOMA-β index, indicating basal insulin release, was significantly reduced by −17% in isolated IFG \( (P = 1.2 \times 10^{-20}) \), whereas it was increased by 33% in isolated IGT \( (P = 1.3 \times 10^{-11}) \), compared with NGT. All categories of glucose tolerance status differed significantly with respect to all other indexes of insulin secretion examined, as shown in Table 4.

**Disposition index.** The early-phase DI30 was lower in isolated IGT than in isolated IFG (−36 vs. −29%) compared with NGT, \( P = 0.0003 \). In the IFG + IGT group, DI30 was decreased by −53%, and in newly diagnosed type 2 diabetic subjects by −68% (Fig. 4F). In contrast, the total DI120 was decreased to the same extent in isolated IFG and isolated IGT (both −27%). DI120 was reduced significantly in the IFG + IGT group by −44% and in newly diagnosed type 2 diabetic subjects by −62% (Fig. 4F).

All statistical analyses were also performed using a cutoff point of 6.1 mmol/l (110 mg/dl) for FPG. All results were essentially similar (supplemental Tables 1 and 2, supplemental Fig. 3).

**DISCUSSION**

Our study is the largest population-based study focusing on the pathophysiology of pre-diabetes using validated surrogate markers for insulin sensitivity and insulin release. This allowed us to perform a detailed analysis on the changes in insulin sensitivity and insulin secretion from normal glucose levels to the diabetic range of hyperglycemia. We demonstrated that insulin sensitivity was already decreased comparably in both nonobese and obese individuals by −37 and −36%, respectively, within the 2-h PG range from 5.0 to 7.9 mmol/l. Thus, our findings suggest that obesity does not affect insulin sensitivity related to hyperglycemia. In another study \( (n = 148) \), Ahren (27) reported decreased insulin sensitivity (−14%) measured by clamp in postmenopausal normoglycemic women within the highest quartile of FPG.

The mechanisms leading to a decrease in insulin sensitivity within the normal range of FPG and 2-h PG remain unclear. Although high glucose (20 mmol/l) and/or high insulin levels decrease glucose uptake in human adipose cells in vitro (37), it is not known whether this effect could be observed at moderately increased glucose concentrations in vivo. Furthermore, our results show that despite a substantial decrease in peripheral insulin sensitivity (−37%), 2-h PG could be maintained within the normal range by a compensatory increase in total insulin release.

The pattern of changes in early-phase insulin release differed from that of insulin sensitivity. The decrease was small in the normal range (approximately −5%), progressed within the IFG and IGT range, and was substantial within the diabetic range (reaching −70% and −51% for diabetic FPG and 2-h PG, respectively). The defect in early insulin response manifested at lower glucose levels than the defect in total insulin response. Previous studies \( (13,25,26,28) \) have not assessed the effect of obesity on the...
relationship between glucose levels and insulin secretion. We showed that both early-phase and total insulin release were substantially higher in obese subjects than in non-obese subjects within the normal range of FPG and 2-h PG (by ~50–70%), but there was no significant interaction between obesity and glucose levels in determining insulin release. Therefore, obesity does not seem to have a major impact on further changes in insulin release in hyperglycemia. Accordingly, Camastra et al. (38) have observed that the dynamic aspects of β-cell response to glucose were unaltered in the morbidly obese non-diabetic subjects.

Previous studies have been inconsistent with respect to differences in insulin sensitivity between isolated IFG and isolated IGT. Decreased peripheral insulin sensitivity in subjects with isolated IGT compared with subjects with isolated IFG has been reported in some studies using the clamp method or IVGTT (9,10,12,14), but also similar impairment in insulin action has been found in both isolated IFG and isolated IGT in Pima Indians (13) and obese Chinese subjects.
In two studies, the decrease in insulin sensitivity in isolated IGT compared with isolated IFG was related to obesity (11,17). In our study, peripheral insulin sensitivity was significantly more reduced in isolated IGT than in isolated IFG (−30% vs. −26%, \( P = 0.0016 \)) and similarly in nonobese and obese subjects (−27 and −31%) with isolated IGT, indicating that the reduction in peripheral insulin sensitivity in isolated IGT was not explained by obesity.

Conflicting findings have been published on 1/HOMA-IR as an index of hepatic insulin sensitivity (11,12,14,18–23). In our study, 1/HOMA-IR was more reduced in isolated IFG than in isolated IGT (−31% vs. −16%). However, HOMA-IR also reflects peripheral insulin sensitivity, and therefore reliable results on hepatic insulin sensitivity can be obtained only by using the tracer technique (13,39).

We observed a small reduction in early-phase insulin release (−8%) but not in isolated IGT,
TABLE 4

| Glucose Tolerance Category | NGT | Isolated IFG | Isolated IGT | IFG | Newly diagnosed diabetes |
|---------------------------|-----|--------------|--------------|-----|-------------------------|
| **P** values**<sup>1</sup>** | 0.002 | 0.002 | 0.001 | 0.001 | 0.001 |
| **Data are medians (25th–75th percentile). Variables with nonnormal right-skewed distribution were logarithmically transformed before analyses.**

**P** values are based on the general linear model adjusted for age and BMI. DI<sub>30</sub> = Matsuda ISI<sub>30</sub>/GluAUC<sub>30</sub>; DI<sub>120</sub> = Matsuda ISI<sub>120</sub>/GluAUC<sub>120</sub>. Bonferroni post hoc tests: all pairwise comparisons between the categories of glucose tolerance were significant at **P** = 0.05, except for: * **P** = 0.05 vs. NGT; † **P** = 0.05 vs. isolated IFG; ‡ **P** = 0.05 vs. isolated IGT.

DI<sub>30</sub>, Disposition index; ISI<sub>30</sub>, Insulin sensitivity/resistance; Fasting serum insulin (pmol/l); HOMA-IR (mU/l, mmol/l); QUICKI (mU/l, mg/dl); MCR Stumvoll (pmol/l, mmol/l); ISI Stumvoll (pmol/l, mmol/l); Matsuda ISI (mU/l, mg/dl).
focusing on FPI and 2-h glucose levels. Peripheral insulin resistance was a predominant feature of isolated IGT, whereas impaired insulin secretion characterized isolated IFG.

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