Insulin Secretion and Insulin Sensitivity in Relation to Glucose Tolerance

Lessons from the Botnia Study

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Recently, a new stage in glucose tolerance, impaired fasting glucose (IFG) (fasting plasma glucose level of 6.1–6.9 mmol/l), was introduced in addition to impaired glucose tolerance (IGT) (2-h glucose level of 7.8–11.0 mmol/l). It is not clear whether IFG and IGT differ with respect to insulin secretion or sensitivity. To address this question, we estimated insulin secretion (by measuring both insulin levels and the ratio of insulin-to-glucose levels in 30-min intervals) and insulin sensitivity (by using the homeostasis model assessment [HOMA] index) from an oral glucose tolerance test (OGTT) in 5,396 individuals from the Botnia Study who had varying degrees of glucose tolerance. There was poor concordance between IFG and IGT: only 36% (303 of 840) of the subjects with IFG had IGT, whereas 62% (493 of 796) of the subjects with IGT did not have IFG. Compared with subjects with normal glucose tolerance (NGT), subjects with IFG were more insulin resistant (HOMA–insulin resistance [IR] values 2.64 ± 0.08 vs. 1.73 ± 0.03, $P < 0.0005$), had greater insulin responses during an OGTT ($P = 0.0001$), had higher waist-to-hip ratios ($P < 0.005$), had higher triglyceride and total cholesterol concentrations ($P < 0.0005$), and had lower HDL cholesterol concentrations ($P = 0.0001$). Compared with subjects with IFG, subjects with IGT had a lower incremental 30-min insulin-to-glucose area during an OGTT (13.8 ± 1.7 vs. 21.7 ± 1.7, $P = 0.0008$). Compared with subjects with IGT, subjects with mild diabetes (fasting plasma glucose levels <7.8 mmol/l) showed markedly impaired insulin secretion that could no longer compensate for IR and elevated glucose levels. A progressive decline in insulin sensitivity was observed when moving from NGT to IGT and to subjects with diabetes ($P < 0.05$ for trend), whereas insulin secretion followed an inverted ∪-shaped form. We conclude that IFG is characterized by basal IR and other features of the metabolic syndrome, whereas subjects with IGT have impaired insulin secretion in relation to glucose concentrations. An absolute decompensation of β-cell function characterizes the transition from IGT to mild diabetes. *Diabetes* 49:975–980, 2000

The American Diabetes Association (ADA) (1) and the World Health Organization (WHO) (2) recently revised the criteria for the diagnosis and classification of diabetes and glucose intolerance. The major revision involved lowering the diagnostic value for the fasting plasma glucose (FPG) level from 7.8 to 7.0 mmol/l, because the latter level was considered to be a better predictor of the risk of microvascular complications (3,4). An FPG level of 7.0 mmol/l showed similar sensitivity as a predictor of retinopathy to the 2-h glucose value of 11.1 mmol/l (5).

Subjects with impaired glucose tolerance (IGT) are at an increased risk of developing diabetes and cardiovascular disease (6–9). However, diagnosis of IGT requires an oral glucose tolerance test (OGTT), the use of which was abandoned by the ADA. Instead, a new stage of impaired fasting glucose (IFG) (6.1–6.9 mmol/l) was introduced to replace IGT. There is, however, little information regarding the predictive value of IFG. Several studies have shown that, by considering only the fasting glucose levels, a large proportion of subjects with IGT are overlooked (10–13).

There is considerable controversy regarding the relative importance of insulin resistance (IR) and abnormal insulin secretion in the pathogenesis of IGT (14–16). Some studies have proposed that loss of early insulin response to glucose and poor suppression of hepatic glucose output are primarily responsible for postprandial hyperglycemia associated with IGT (17). In contrast, under experimental conditions, defective insulin action was shown to contribute more to postprandial hyperglycemia than defective insulin secretion (18). Because only a portion of these previous subjects with IGT have elevated fasting glucose concentrations, it is not known whether the subjects with IFG show the same metabolic disturbances as the subjects with IGT. To address these questions, we assessed insulin secretion (by measuring incremental 30-min insulin responses during an OGTT) and insulin sensitivity (using a homeostasis model assessment [HOMA]), with particular emphasis on contrasting IFG with IGT, in 5,396 subjects with varying degrees of glucose tolerance.

RESEARCH DESIGN AND METHODS

The Botnia Study (19) was established in 1990 to identify the genetic and metabolic factors contributing to the pathogenesis of type 2 diabetes in families from the western coast of Finland. The prevalence of diabetes in this region is ~3% with 85% having type 2 diabetes. All patients with known type 2 diabetes (response rate was 90%) and their available family members (response rate ~70%) from 4 primary care centers in the Botnia region were invited to participate in the study. The study was subsequently extended to other parts of Finland and Sweden with the aim to include families with at least 2 members with type 2 diabetes. Subjects were classified into different stages of glucose tolerance based on their fasting and 2-h plasma glucose concentrations. IFG was defined as having an FPG level between 6.1 and 6.9 mmol/l and a 2-h glucose level <7.8 mmol/l. IGT was defined as having an FPG level <6.1 mmol/l and a 2-h glucose value between 7.8 and 11.1 mmol/l. Subjects with FPG levels of 6.1–6.9 mmol/l and 2-h glucose values of 7.8–11.1 mmol/l were considered IFG/IGT. Subjects with FPG levels of 7.0–7.7 mmol/l were considered to have mild diabetes. Body weight and height were measured while subjects wore light clothing without shoes. Waist circumference was measured with a soft tape on standing subjects midway between the lowest rib and the iliac crest. Hip circumference was measured over the widest part of the gluteal region, and waist-to-hip ratio (WHR) was accordingly calculated. Samples for the measurement of HbA$_{1c}$, cholesterol, HDL cholesterol, and triglyceride levels were drawn after an overnight fast. A standard (75-g) OGTT was performed in all of the subjects attending the clinic and in only those diabetic subjects whose FPG level was <11 mmol/l. Blood samples for the determination of blood glucose and serum insulin levels were drawn at –10, 0, 30, 60, and 120 min.

As indexes of insulin secretion, we used the early incremental insulin response during an OGTT (I30) and the change in the ratio of insulin-to-glucose levels during the first 30 min of the OGTT (I/G30).

As measures of insulin sensitivity, we used the fasting serum insulin concentration and the HOMA-IR index (20) as

$$\frac{\text{FPG (mmol/l)} \times \text{fasting insulin (mU/l)}}{22.5}$$

Assays. Plasma glucose was measured with a glucose oxidase method using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Serum insulin concentrations were measured in duplicates by a radioimmunoassay (Pharmacia, Sweden) with an intra-assay coefficient of variation of 9%. The serum total cholesterol, HDL cholesterol, and triglyceride concentrations were measured on a Cobas Mira analyzer (Hoffman LaRoche, Basel, Switzerland).
Statistical analysis. Data are expressed as means ± SD or means ± SE. Plasma insulin and glucose values were log-transformed to improve skewness and kurtosis. The area under the insulin curve was calculated using the trapezoidal rule. Differences between the groups were tested by the Student's *t* test and with analysis of variance (ANOVA) after adjustment for BMI and age. Analysis for linear trend was carried out by ANOVA. Multiple regression analysis was performed with fasting and 2-h glucose measurements as dependent variables and with measures of insulin secretion and insulin action; age and BMI were considered independent variables. *P* < 0.05 was considered statistically significant. Data were analyzed using the Number Cruncher Statistical System (NCSS, version 6.0; Statistical Solutions, Cork, Ireland).

RESULTS

Glucose tolerance and clinical characteristics. According to the new WHO criteria, of a total of 5,396 subjects, 3,086 had normal glucose tolerance (NGT), 537 had IFG, 493 had IGT, 303 had IFG/IGT, 302 subjects had mild diabetes (FPG 7.0–7.7 mmol/l), and 675 were classified as having diabetes by using the old criterion of having a fasting glucose level >7.8 mmol/l. Of the 1,333 subjects with impaired glucose metabolism (IFG and/or IGT), only 303 (23%) subjects with IFG also had IGT. Of subjects in the IFG group, 537 (56%) did not have IGT, whereas in the IGT group, 493 (62%) had normal fasting glucose levels. Table 1 shows the clinical characteristics of the different groups. Mean age, BMI, and WHR progressively increased from the normoglycemic to the diabetic subjects (*P* < 0.05 for trend). In addition, triglyceride concentrations increased whereas HDL cholesterol concentrations decreased with a worsening of glucose tolerance (*P* < 0.05 for trend). Subjects with IFG had a higher WHR (*P* < 0.0005 for both men and women) and higher total cholesterol and triglyceride concentrations (*P* < 0.0005) than subjects with NGT.
**Insulin secretion.** Figure 1 shows the insulin response during OGTTs in the 5 groups. The insulin response progressively increased from NGT to IGT and then declined with the onset of manifest hyperglycemia. The insulin profile during the OGTT in patients with IFG was similar to that of NGT subjects, but at higher levels. In contrast, the insulin profile in subjects with IGT resembled the profile in diabetic subjects, but at lower levels. The incremental insulin area during the OGTT was higher in the IFG group (5,336 ± 142 vs. 4,449 ± 59 mU · l^{-1} · h^{-1}, *P* < 0.0005) and the IGT group (6,685 ± 148 vs. 4,449 ± 59 mU · l^{-1} · h^{-1}, *P* < 0.0005) , as compared with the NGT group.

The incremental insulin response during the first 30 min of OGTT was higher in subjects with IFG and IGT compared with that in subjects with NGT, and it started to decline in subjects with mild diabetes (Fig. 2). In contrast, when insulin secretion was expressed relative to the glucose concentration (i.e., as the I/G30), there was a progressive decline in insulin secretion from NGT and IFG to IGT and diabetes (Fig. 3). Even though the IFG and NGT subjects had almost identical I/G30 values, the I/G30 value was significantly lower in IGT subjects compared with IFG subjects (13.8 ± 1.7 vs. 21.7 ± 1.7, *P* = 0.0008).

TABLE 1
Clinical characteristics of subjects with varying degrees of glucose tolerance

	NGT	IFG	IGT	IFG/IGT	Mild diabetes	Diabetes
n	3,086	537	493	303	302	675
M/F (%)	45/55	60/40	40/60	47/53	47/53	48/52
Age (years)*	45.7 ± 15	52.1 ± 13†	56.2 ± 16‡	57.9 ± 14	59.6 ± 13	63.2 ± 11
BMI (kg/m^2)*	25.3 ± 3.8	26.7 ± 4.0†	27.4 ± 4.5‡	28.6 ± 4.5	28.9 ± 5.1	29.3 ± 4.8
WHR*						
Women	0.82 ± 0.07	0.84 ± 0.08†	0.85 ± 0.07	0.85 ± 0.07	0.88 ± 0.07	0.89 ± 0.06
Men	0.94 ± 0.7	0.95 ± 0.6†	0.96 ± 0.05	0.97 ± 0.05	0.97 ± 0.05	0.98 ± 0.06
FPG (mmol/l)	5.31 ± 0.4	6.4 ± 0.2	5.5 ± 0.4	6.5 ± 0.2	7.3 ± 0.2	9.9 ± 1.8
2-h Plasma glucose (mmol/l)	5.7 ± 1.0	6.4 ± 0.9	8.9 ± 0.8	9.0 ± 0.9	11.4 ± 3.8	18.4 ± 5.4
HbA$_{1c}$ (%)*	5.27 ± 0.5	5.48 ± 0.5	5.44 ± 0.6	5.6 ± 0.6	5.98 ± 0.7	7.36 ± 1.2§
Cholesterol (mmol/l)	5.44 ± 1.2	5.77 ± 1.2†	5.84 ± 1.1	5.82 ± 1.1	5.83 ± 1.1	5.76 ± 1.1
Triglyceride (mmol/l)*	1.21 ± 0.7	1.41 ± 0.7†	1.63 ± 0.8	1.74 ± 1.1	1.73 ± 0.9	1.89 ± 1.07
HDL cholesterol (mmol/l)*	1.38 ± 0.4	1.31 ± 0.3†	1.26 ± 0.3	1.25 ± 0.3	1.20 ± 0.3	1.16 ± 0.3

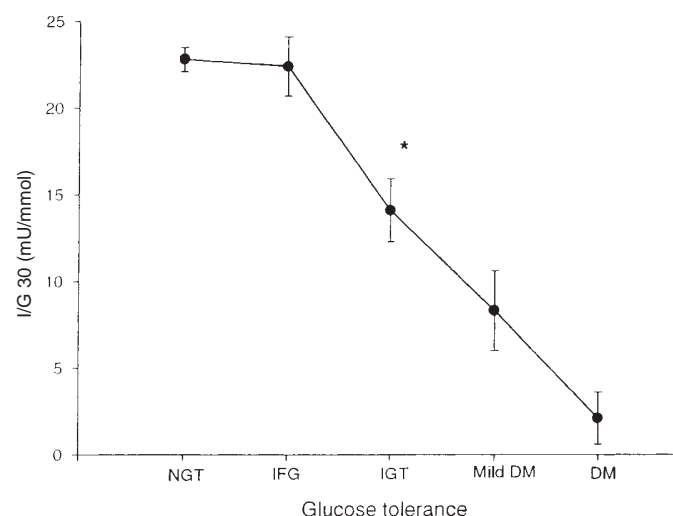Data are means ± SD. *P* < 0.05 for trend; †*P* < 0.05 vs. NGT; ‡*P* < 0.05 vs. IFG; §*P* < 0.05 vs. mild diabetes.
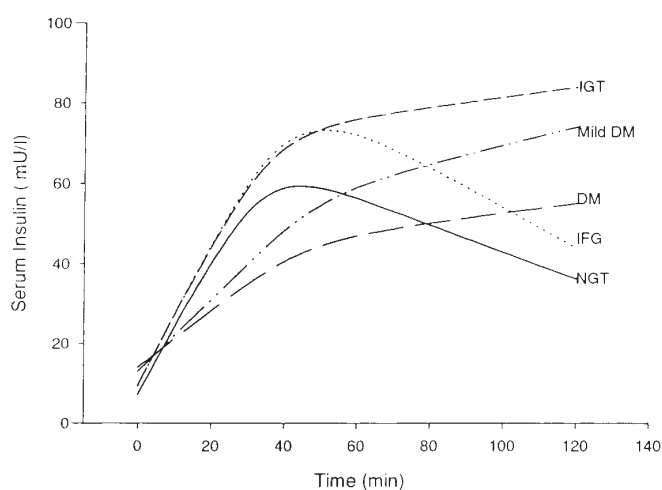
FIG. 1. The insulin response during OGTTs (n = 5,396) in subjects with NGT, IFG, IGT, mild diabetes (Mild DM), and diabetes (DM) (FPG level >7.8 mmol/l). P < 0.0005 for the difference in insulin area in subjects with NGT vs. IFG and in subjects with IFG vs. IGT.

FIG. 3. The I/G30 ratio in subjects with NGT, IFG, IGT, mild diabetes (Mild DM), and diabetes (DM). Data are means ± SE. *P < 0.005 for IGT vs. IFG and NGT.

The insulin area under curve was higher in subjects with both IFG and IGT (7,348 ± 189) than in subjects with only IFG (5,336 ± 142; P < 0.005) or IGT (6,685 ± 148; P = 0.04) (data not shown). The I30 value was also higher in subjects with IFG/IGT (832 ± 28) compared with that in subjects with only IFG (760 ± 21) or only IGT (743 ± 21). However, when measured in relation to the glucose response, the insulin response was lower in IFG/IGT subjects than in IFG subjects (15.6 ± 0.8 vs. 21.7 ± 1.7, P = 0.003).

Insulin sensitivity. Subjects with IFG were more insulin-resistant than subjects with NGT, as indicated by a higher HOMA-IR index (2.64 ± 0.08 vs. 1.73 ± 0.03, P < 0.0005) and a higher fasting insulin concentration (9.09 ± 0.4 vs. 8.2 ± 0.1 mU/l, P < 0.005). There was no significant difference in insulin sensitivity between IFG and IGT subjects (Fig. 4). In addition, subjects with IFG/IGT (3.59 ± 0.12) had higher
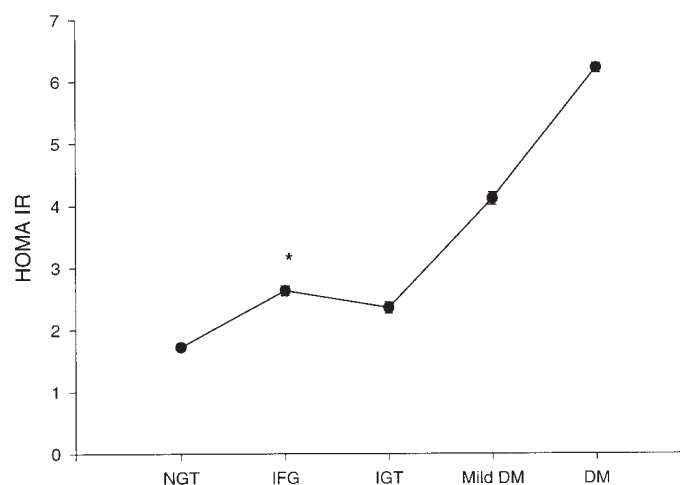
HOMA values than subjects with isolated IFG (2.64 ± 0.08, P < 0.005) or isolated IGT (2.36 ± 0.09, P = 0.005).

Correlation between different measures of insulin secretion and insulin sensitivity and between fasting and 2-h glucose concentrations. To identify determinants of IFG and IGT, we also examined the correlation between measurements of insulin secretion and insulin sensitivity and between measurements of fasting and 2-h glucose concentrations, in both a univariate and a multivariate analysis (Table 2). The early insulin response, either measured as I30 or I/G30, was negatively correlated with both fasting and 2-h glucose levels. An impaired I30 value was a determinant of the 2-h glucose concentration. In a partial regression analysis, IR (HOMA-IR) and insulin secretion (I30) explained 45% of the FPG value (FPG = 5.63 + [0.414 × HOMA-IR] – [0.008 × I30], r^2 = 0.450, P < 0.005) and 39% of the 2-h glucose value (2-h glucose = 6.94 + [1.07 × HOMA-IR] – [0.002 × I30], r^2 = 0.389, P < 0.05).

FIG. 2. The I30 value in relation to glucose tolerance. Data are means ± SE. *P < 0.0005 for NGT vs. IFG and for IGT vs. mild diabetes. DM, diabetes.

FIG. 4. Insulin sensitivity estimated by HOMA. Data are means ± SE. *P < 0.0005 for NGT vs. IFG and for mild diabetes vs. diabetes. DM, diabetes.

TABLE 2
Univariate correlation relating glucose tolerance with measures of insulin sensitivity and insulin secretion and multivariate (multiple linear regression) analysis with fasting plasma glucose and 2-h glucose as dependent variables

	Fasting insulin	I30	I/G30	HOMA-IR
Univariate FPG				
r	0.448	−0.186	−0.174	—
P	$<10^{-5}$	0.001	0.003	—
Multivariate FPG				
β	−0.009	−0.001	−0.003	—
Standardized coefficient	0.340	−0.313	−0.007	—
P	<0.0001	<0.0001	0.512	—
Univariate 2-h glucose				
r	0.431	−0.179	−0.165	0.594
P	$<10^{-5}$	0.002	0.005	<0.0001
Multivariate 2-h glucose				
β	−0.805	−0.001	−0.003	2.43
Standardized coefficient	−1.022	−0.190	−0.03	1.279
P	<0.0001	<0.0001	0.001	<0.0001

Age and BMI were included in the model for analysis of each independent variable. β, Regression coefficient; r, correlation coefficient.

DISCUSSION

Our results clearly demonstrate that IFG and IGT represent 2 different populations with disturbed glucose metabolism. In these populations, the contributions of β-cell dysfunction and IR to the development of glucose intolerance differ. Only 36% of subjects with IFG also had elevated 2-h glucose values, whereas 38% of the IGT subjects had elevated fasting glucose levels. Thus, if only the fasting glucose levels are considered, then 37% of the subjects with isolated abnormalities in 2-h values (IGT) will be overlooked. Our data are in accordance with several recent reports of various ethnic groups (10–13) that reflected poor concordance between IFG and IGT.

Although there is general agreement that subjects with overt type 2 diabetes have β-cell dysfunction, the stage in the evolution of glucose intolerance at which this dysfunction develops is uncertain. A number of studies have suggested that defective insulin action is the major identifiable defect present in subjects at risk for type 2 diabetes (22–24) and that β-cell function becomes abnormal only when the fasting plasma glucose levels are elevated (25,26). On the other hand, there is also evidence that defective insulin secretion may be present before the onset of overt diabetes (27,28).

In the present study, the I30 value was slightly higher in both IFG and IGT subjects than in NGT subjects. These data from a large number of subjects are thus in contrast to the finding of a 40% lower I30 value, as previously reported in a study of IGT subjects (17). In contrast, we were not able to show an inverse correlation between the early insulin response and the 2-h glucose level in the nondiabetic subjects. However, in all of the subjects (including the patients with diabetes), the I30 value explained 39% of the variance in the 2-h glucose value. Adjusting the insulin response for the ambient glucose concentration did not change these results.

HOMA-IR indexes were significantly worse in the IFG subjects compared with the NGT subjects ($P < 0.00005$). Hence, it seems that the major determinant of IFG is defective insulin action rather than impaired β-cell function. Of note, IFG subjects in the present study had a normal 2-h glucose value (6.4 ± 0.02 mmol/l). In the postabsorptive state, the majority of glucose uptake occurs in insulin-independent tissues (29). Consequently, the fasting glucose level is largely determined by the endogenous glucose production (30). Thus, subjects with predominant defects in hepatic insulin sensitivity are likely to present with fasting hyperglycemia (IFG). HOMA values are derived in the basal state and can therefore be considered to reflect basal or hepatic insulin sensitivity. Although we have not directly measured hepatic glucose output, HOMA data may serve as a surrogate for hepatic insulin sensitivity. It is noteworthy that in addition to IR, subjects with IFG, as compared with subjects with NGT, showed significantly elevated triglyceride and total cholesterol concentrations and lower HDL cholesterol concentrations. These features, along with the elevated WHR, suggest that IFG subjects show several features of the metabolic syndrome and can be considered to be at high risk of diabetes and coronary heart disease (31).

Subjects with IGT had a lower I/G30 response than subjects with IFG. A low I/G30 value has been reported in IGT subjects (32), and it has been shown to predict both the development of diabetes in subjects with IGT and the progression from NGT to IGT (15,33,34). Although the precise nature of β-cell dysfunction in IGT remains unclear, prolonged hyperinsulinemia, as a result of either primary hypersecretion or IR, can lead to the exhaustion of a predisposed β-cell (35). The progressive worsening in metabolic profiles when moving from IFG to IGT suggests that IFG and IGT represent 2 different stages in the natural history of the development of diabetes (IGT is closer to the end point diabetes than IFG). In this regard, it is relevant to note the recent report of a higher predictive value of IGT versus IFG for future diabetes (36).

There was a marked decline in β-cell function when moving from normal to diabetic glucose tolerance. It is worth noting that the HOMA-IR increased 3.6-fold at the same time, significantly more than the 30% decline in insulin sensitivity observed in a progressive study of 17 Pima Indians who progressed from NGT to manifest diabetes (21). This change in insulin sensitivity is of the same magnitude as the change we observed when using the euglycemic clamp in a smaller number of subjects (data not shown). The estimation of HOMA-IR is based on the assumption of a normal feedback loop between the liver and the pancreatic β-cells (20). How-

ever, this is not always the case in diabetic subjects. On the other hand, the euglycemic clamp circumvents the problem by measuring tissue sensitivity to a steady-state concentration of exogenous insulin. It is apparent that with the onset of hyperglycemia, the HOMA values are more influenced by the fasting glucose levels than by insulin sensitivity per se and may overestimate IR.

Whereas IGT was characterized by impaired insulin secretion relative to glucose and the degree of IR, mild diabetes was characterized by marked impairment of β-cell function. This means that the decompensation phase of the Starling's curve of β-cell function (37) occurs at the 2-h plasma glucose concentration of ~9.5–10 mmol/l. Most subjects with IGT with 2-h values above this level will develop diabetes (38). In addition, this level has also been used as an indication to start insulin therapy in patients with gestational diabetes (39). Consequently, questions have been raised concerning whether the diagnosis of diabetes by use of 2-h glucose values should be based on biochemical evidence of hormone (insulin) deficiency in analogy with other endocrine disorders. To do so would require lower 2-h values than those previously used.

It can be argued that the results in the present study might have been influenced by the presence of a family history of diabetes (19). However, all of the individuals in the study came from families with type 2 diabetes, and we did not a priori test the influence of a family history of diabetes.

In terms of limitations, the study's cross-sectional design does not provide insight into the time course of the development of abnormalities in insulin secretion or action. It can also be argued that the progressive decline in insulin secretion and insulin sensitivity may partly be an age-related phenomenon (40); however, the measures of insulin secretion and insulin action were adjusted for both age and BMI. In conclusion, only 36% of subjects with IFG also had elevated 2-h glucose values that were compatible with IGT. IFG is characterized by basal IR, as indicated by elevated HOMA-IR values, and features of the metabolic syndrome, including high WHR, elevated triglyceride and total cholesterol concentrations, and low HDL cholesterol concentrations. Subjects with IGT differed from subjects with IFG with respect to impaired insulin secretion relative to the level of glycemia and to the degree of insulin sensitivity. An absolute decompensation in β-cell function was seen while moving from IGT to subjects with mild diabetes.

ACKNOWLEDGMENTS

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