Disturbances in β-Cell Function in Impaired Fasting Glycemia

Timon W. van Haeften,[1] Walkyria Pimenta,[2] Asimina Mitrakou,[3] Mary Korytkowski,[4] Trond Jenssen,[5] Hannele Yki-Jarvinen,[6] and John E. Gerich[7]

In a cross-sectional study, we assessed β-cell function and insulin sensitivity index (ISI) with hyperglycemic clamps (10 mmol/l) in 24 subjects with impaired fasting glycemia (IFG, fasting plasma glucose [FPG] between 6.1 and 7.0 mmol/l), 15 type 2 diabetic subjects (FPG >7.0 mmol/l), and 280 subjects with normal fasting glycemia (NFG, FPG <6.1 mmol/l). First-phase insulin release (0–10 min) was lower in IFG (geometric mean 541 pmol/l · 10 min; 95% confidence interval [CI] 416–702 pmol/l · 10 min) and in type 2 diabetes (geometric mean 376 pmol/l · 10 min; 95% CI 247–572 pmol/l · 10 min) than NFG (geometric mean 814 pmol/l · 10 min; 95% CI 759–873 pmol/l · 10 min) ($P < 0.001$). Second-phase insulin secretion (140–180 min) was also lower in IFG (geometric mean 251 pmol/l; 95% CI 198–318 pmol/l; $P = 0.026$) and type 2 diabetes (geometric mean 157 pmol/l; 95% CI 105–235 pmol/l; $P < 0.001$) than NFG (geometric mean 295 pmol/l; 95% CI 276–315 pmol/l). IFG and type 2 diabetic subjects had a lower ISI (0.15 ± 0.02 and 0.16 ± 0.02 μmol/kg fat-free mass [FFM]/min/pmol/l, respectively) than NFG (0.24 ± 0.01 μmol/kg FFM/min/pmol/l, $P < 0.05$). We found a stepwise decline in first-phase (and second-phase) secretion in NFG subjects with progressive decline in oral glucose tolerance ($P < 0.05$). IFG subjects with impaired glucose tolerance (IGT) had lower first-phase secretion than NFG subjects with IGT ($P < 0.02$), with comparable second-phase secretion and ISI. NFG and IFG subjects with a diabetic glucose tolerance (2-h glucose >11.1 mmol/l) had a lower ISI than their respective IGT counterparts ($P < 0.05$). We conclude that the early stages of glucose intolerance are associated with disturbances in β-cell function, while insulin resistance is seen more markedly in later stages. *Diabetes* 51 (Suppl. 1):S265–S270, 2002

From the [1]Department of Internal Medicine, University Medical Center Utrecht, Utrecht, the Netherlands; the [2]Department of Internal Medicine, Estadual Paulista University, Botucatu, Brazil; the [3]Diabetes Center Henry Dunant, Athens, Greece; the [4]Department of Endocrinology, University of Pittsburgh, Pittsburgh, Pennsylvania; the [5]Department of Internal Medicine, Oslo University, Oslo, Norway; the [6]Department of Diabetes, University of Helsinki, Helsinki, Finland; and the [7]Department of Endocrinology, University of Rochester, Rochester, New York.

Address correspondence and reprint requests to t.w.vanhaeften@azu.nl.

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DGT, diabetic glucose tolerance; FFM, fat-free mass; FPG, fasting plasma glucose; GIR, glucose infusion rate; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; NFG, normal fasting glycemia; ISI, insulin sensitivity index; LBM, lean body mass; OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio.

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Recently, the diagnostic criteria for diabetes mellitus have been adapted by the American Diabetes Association (ADA), and the new entity impaired fasting glycemia (IFG) has been introduced (1). Subjects with IFG have a fasting plasma glucose level between 6.1 and 7.0 mmol/l. This entity was introduced to underline the (potential) importance of a slight elevation in (fasting) glycemia as a risk factor for (later) development of type 2 diabetes. Subjects with type 2 diabetes mellitus have been shown to have abnormalities in both insulin secretion and insulin sensitivity; such abnormalities are risk factors for later development of type 2 diabetes (2,3). Whether one of them precedes the other is still an important topic of discussion (4), although recent studies from our group have found that first-degree relatives of Caucasian type 2 diabetic subjects have an impairment in β-cell function (5,6). We have recently reported that Caucasian subjects with impaired glucose tolerance (IGT) have a diminished β-cell function as compared to subjects with normal glucose tolerance (NGT) (7,8). The question arises in what respect impairment in fasting glycemia (in both the diabetic and the nondiabetic ranges) relates to IGT with respect to β-cell function and tissue insulin (in)sensitivity. More specifically, the relative importance of β-cell function and tissue insulin sensitivity for various degrees of impairment of fasting glycemia for subjects who fulfill 2-h postglucose load criteria for IGT or type 2 diabetes mellitus is unclear.

The delineation of, on the one hand, three categories of *fasting glycemia* (normal fasting glycemia [NFG], IFG, and type 2 diabetes) and, on the other hand, three subcategories of subjects according to *2-h postglucose load glycemia* (NGT [2-h plasma glucose <7.8 mmol/l], IGT [2-h plasma glucose between 7.8 and 11.1 mmol/l], or diabetic glucose tolerance [DGT, 2-h plasma glucose >11.1 mmol/l]) offers a further tool to study the importance of changes in β-cell function and insulin sensitivity for the development of type 2 diabetes mellitus, by careful comparison of the various potential subgroups. Subjects with fasting hyperglycemia (type 2 diabetes, plasma glucose >7.0 mmol/l) were not further subdivided since they already fulfilled the criteria for type 2 diabetes mellitus. Therefore, this subdivision according to the two categories leads to seven subgroups.

In the present studies, we addressed the following questions: in subjects with NFG (plasma glucose <6.1 mmol/l), are there differences in biographic data (age,

overweight, and fat distribution) or in β-cell function and tissue insulin sensitivity between subjects with 2-h criteria for NGT, IGT, or DGT)? Similarly, in subjects with IFG, are there differences in biographic data and/or β-cell function and tissue insulin sensitivity between subjects who fulfill the criteria for NGT, IGT, or DGT, according to 2-h postglucose load glycemia? Conversely, these studies also address what determines fasting glycemia level (NFG or IFG) in subjects with IGT.

The hyperglycemic clamp is generally accepted for the assessment of β-cell function under standard conditions. Mitrakou et al. (9) compared the insulin sensitivity index (ISI) determined with a hyperglycemic glucose clamp with the ISI determined with a euglycemic hyperinsulinemic glucose clamp in the same subjects, and found a good agreement between the two methods. They proposed the use of the hyperglycemic glucose clamp for both β-cell function and the assessment of the ISI.

For these studies, we determined fasting glycemia and glucose tolerance (standard 75-g oral glucose tolerance test [OGTT]) in 319 consecutive subjects who were not known to have diabetes, and assessed β-cell function and ISI (a measure of tissue insulin sensitivity) with a 180-min hyperglycemic glucose clamp.

RESEARCH DESIGN AND METHODS

Subjects. A total of 319 healthy subjects took part in this ongoing multicenter study. Subjects were recruited by advertisement. The study had been approved by the local ethics committees, and after the nature of the study had been explained to each participant, informed written consent was obtained. Data from some of these subjects have been previously reported (5–10), except for the subjects with postglucose hyperglycemia (plasma glucose >11.1 mmol/l) and the subjects with fasting hyperglycemia (plasma glucose >7.0 mmol/l).

All subjects had normal values for routine laboratory measurements for hematology, lipids, and kidney, liver, and thyroid function. Lean body mass (LBM) or fat-free mass (FFM) was calculated according to Hume's formula (11).

Glucose measurements. Fasting glucose level was the average of two measurements at separate occasions at least 1 week apart. Subjects were divided into the categories NFG (average fasting glucose level <6.1 mmol/l), IFG (average fasting glucose between 6.1 and 7.0 mmol/l), and type 2 diabetes (average fasting glucose >7.0 mmol/l).

An OGTT was performed as previously described (5,6) using 75 g glucose in 300 ml water. Blood samples for glucose and insulin determinations were taken at 0, 30, 60, 90, and 120 min.

A hyperglycemic glucose clamp test was performed as previously described (6); arterialized venous blood glucose was maintained at 10 mmol/l (coefficient of variation around 3%) with variable infusion with 20% glucose. Blood samples for insulin determination were taken at points specified in Fig. 1. The glucose infusion rate (GIR) was assessed during the clamps.

Laboratory measurements. Plasma insulin was determined by radioimmunoassay as previously described (5,6).

Calculations. Subjects were classified according to fasting glycemia (see above) into categories of NFG, IFG, or type 2 diabetes. The NFG and IFG groups were subdivided according to 2-h postglucose load glycemia into subcategories of NGT (2-h plasma glucose <7.8 mmol/l), IGT (2-h plasma glucose between 7.8 and 11.1 mmol/l), and DGT (2-h plasma glucose >11.1 mmol/l).

Logarithmic transformation for plasma insulin was used since plasma insulin levels showed a log-normal distribution. The first and second phases of insulin secretion were taken as the sum of plasma insulin levels from 2.5 to 10 min and as the average plasma insulin from 140 to 180 min during the hyperglycemic clamp, respectively. The ISI was defined as the GIR necessary to maintain the hyperglycemic clamp from 120 to 180 min (expressed as μmol · kg LBM^{-1} · min^{-1}) divided by the mean plasma insulin level of the third hour (expressed as pmol/l).

Statistical analysis. Data are presented as means ± SE. Plasma insulin levels were log-transformed for analyses, since they had a log-normal distribution, and are presented as geometric mean with 95% confidence intervals (CI) (12).

ANOVA was performed with and without the use of age, gender, BMI, and waist-to-hip ratio (WHR) as covariates, since they affect insulin secretion and insulin sensitivity. ANOVA for β-cell function was also performed with the use of ISI as a covariate, since insulin sensitivity is known to influence insulin secretion (13).

Multiple linear regression was performed on the relationships of parameters of β-cell function (after log-transformation) and ISI, on the one hand, and age, gender, BMI and WHR, on the other. Adjusted data for β-cell function (after transformation back from the logarithmic value) and for ISI were calculated for the six groups with diminished glucose tolerance; the actual data for β-cell function and ISI were expressed as percentage of the "predicted" value in order to gain a better insight in the disturbances in β-cell function and ISI.

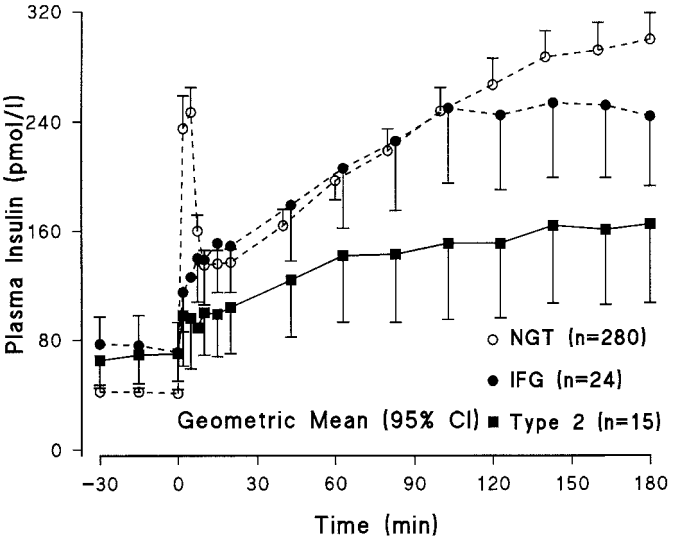

FIG. 1. Geometric mean (95% CI) plasma insulin levels during 180-min hyperglycemic glucose clamps (10 mmol/l) in 280 NGT subjects, 24 IFG subjects, and 15 type 2 diabetic subjects.

RESULTS

Fasting glycemia and glucose tolerance. The 319 subjects studied were subdivided into three categories on the basis of their fasting plasma glucose level: 280 had NFG, 24 had IFG, and 15 had fasting hyperglycemia in the range of type 2 diabetes (glucose >7.0 mmol/l). Subjects in the categories NFG and IFG were further subdivided according to glucose tolerance, which led to the subdivision into seven subgroups, as mentioned in Table 1. Since only two subjects fell into the category of IFG/NGT, their data were not used for statistical analysis.

Physical characteristics. As shown in Table 1, subjects with NFG were younger than subjects with IFG, which achieved statistical significance for comparisons of NFG/IGT, IFG/IGT, IFG/DGT, and type 2 diabetes with NFG/NGT (all $P < 0.02$). Similarly, the NFG/IGT, IFG/IGT, IFG/DGT, and type 2 diabetic subjects also had a higher WHR than their NFG/NGT counterparts. However, BMI was statistically significantly increased only in NFG/IGT subjects as compared with NFG/NGT. As expected, HbA_{1c} was higher in IFG and type 2 diabetic subjects.

β-Cell function. Plasma insulin levels during the clamps are depicted in Fig. 1. First-phase secretion was lower during the hyperglycemic glucose clamp in IFG (geometric mean 541 pmol/l; 95% CI 416–702 pmol/l) and type 2 diabetes (geometric mean 376 pmol/l; 95% CI 247–572

TABLE 1
Clinical and metabolic characteristics of subjects divided into categories of normal (NFG) and impaired fasting glycemia (IFG), and subdivided according to glucose tolerance (normal glucose tolerance [NGT], impaired glucose tolerance [IGT], and diabetic glucose tolerance [DGT]); and subjects with type 2 diabetes according to fasting hyperglycemia (plasma glucose > 7.0 mmol/l).

	NFG			IFG			Type 2 diabetes
	NFG/NGT	NFG/IGT	NFG/DGT	IFG/NGT	IFG/IGT	IFG/DGT	
n	184	86	10	2	9	13	15
Gender	61 M/123 F	31 M/55 F	3 M/7 F	2 M/0 F	7 M/2 F	7 M/6 F	13 M/2 F
Age (years)	43.1 ± 0.8	48.8 ± 1.2*	47.7 ± 2.9	36	52.1 ± 3.4‡	54.3 ± 2.2§	51.7 ± 2.5***
BMI (kg/m^2)	26.1 ± 0.3	28.0 ± 0.6*	25.7 ± 1.2	28.8	28.2 ± 1.2	28.5 ± 1.3	25.6 ± 0.6&
WHR	0.82 ± 0.01	0.87 ± 0.01*	0.86 ± 0.02	0.91	0.94 ± 0.03#‡	0.91 ± 0.02§	0.92 ± 0.01§***
HbA_{1c} (%)	5.10 ± 0.04	5.55 ± 0.06*	6.42 ± 0.21¶†	5.3	5.77 ± 0.19‡	6.23 ± 0.24§	6.55 ± 0.22***&
FPG (mmol/l)	5.2 ± 0.03	5.4 ± 0.10*	5.6 ± 0.12¶	6.3	6.5 ± 0.10##‡	6.6 ± 0.07§**	7.6 ± 0.12***&&
2-h PG (mmol/l)	5.9 ± 0.08	8.9 ± 0.10*	12.5 ± 0.48¶†	6.0	9.5 ± 0.35‡	12.9 ± 0.40$§	13.6 ± 0.79***&&

Data are means ± SEM. NFG/NGT versus NFG/IGT: *$P < 0.01$; NFG/IGT versus NFG/DGT: †$P < 0.001$; NFG/IGT versus IFG/IGT: #$P = 0.022$, ##$P < 0.001$; NFG/NGT versus NFG/DGT: ¶$P < 0.005$; NFG/NGT versus type 2: ***$P < 0.005$; NFG/DGT versus IFG/DGT: **$P < 0.001$; NFG/DGT versus type 2: §$P = 0.028$; NFG/NGT versus IFG/IGT: ‡$P < 0.02$; IFG/IGT versus type 2: &$P = 0.042$, &&$P < 0.005$; NFG/NGT versus IFG/DGT: §$P < 0.001$; IFG/IGT versus IFG/DGT: $$P < 0.001$. PG, plasma glucose.

pmol/l) than in NFG (geometric mean 814 pmol/l; 95% CI 759–873 pmol/l; both $P < 0.001$); the difference between type 2 diabetes and IFG was not statistically significant ($P = 0.12$). When gender, age, BMI, and WHR or ISI were used as covariates, almost identical results were obtained.

Second-phase secretion was not statistically lower in IFG (geometric mean 251 pmol/l; 95% CI 198–318 pmol/l) than in NFG (geometric mean 295 pmol/l; 95% CI 276–315 pmol/l, $P = 0.18$), but use of gender, age, BMI, and WHR ($P = 0.026$) or ISI ($P = 0.009$) as covariates showed significant differences. Second-phase secretion was also lower in type 2 diabetes (geometric mean 157 pmol/l; 95% CI 105–235 pmol/l) than in NFG regardless of covariates ($P < 0.001$).

The difference between type 2 diabetes and IFG ($P = 0.034$) disappeared when gender, age, BMI, and WHR were used as covariates.

Tissue insulin sensitivity. The ISI was lower in IFG than in NFG ($P = 0.038$), but the difference disappeared when gender, age, BMI, and WHR were used as covariates. ISI was lower in type 2 diabetic subjects than in NFG, regardless of inclusion of covariates (both $P < 0.05$), but not lower than in IFG (both $P > 0.50$).

Categories of glucose tolerance

Normal fasting glycemia.

β-Cell function. First-phase secretion showed a progressive decline in the categories NFG/IGT and NFG/DGT, regardless of the inclusion of gender, age, BMI, WHR, or ISI as covariates (all $P < 0.002$; Table 2). For second-phase secretion, there was also a decline between NFG/NGT and NFG/IGT, regardless of the inclusion of covariates (all $P < 0.002$). The difference between NFG/IGT and NFG/DGT was less clear ($P = 0.023$), but was clearly related to ISI, since use of ISI as covariate showed a marked difference ($P < 0.001$).

Tissue insulin sensitivity. The ISI was decreased in both subjects with NFG/IGT and subjects with NFG/DGT, as compared to NFG/NGT (both $P = 0.038$), without a difference between NFG/IGT and NFG/DGT ($P = 0.31$). When gender, age, BMI, and WHR were used as covariates, ISI was still lower in NFG/DGT than NFG/NGT ($P = 0.036$) and NFG/IGT ($P = 0.023$), while the difference between NFG/IGT and NFG/NGT was completely lost ($P = 0.94$).

IFG. Since only two subjects with IFG/NGT were seen, they were not included in the statistical analysis.

β-Cell function. First- and second-phase secretion were not different between the IFG/IGT and IFG/DGT sub-

TABLE 2
Indices of insulin secretion and insulin sensitivity in subjects with normal fasting glucose (NFG) and impaired fasting glucose (IFG), subdivided according to oral glucose tolerance test (OGTT), and subjects with type 2 diabetes, according to fasting hyperglycemia (glucose > 7.0 mmol/l).

	NFG			IFG			Type 2 diabetes
Fasting glycemia	NFG/NGT	NFG/IGT	NFG/DGT	IFG/NGT	IFG/IGT	IFG/DGT	
n	184	86	10	2	9	13	15
Insulin secretion							
First phase (pmol/l)	900 (835–971)	724 (630–832)*	351 (253–480)¶†††	1,179	467 (302–720)‡‡#	530 (367–767)§	376 (247–572)**
Second phase (pmol/l)	323 (301–346)	260 (227–299)*	159 (114–223)¶†	513	221 (139–351)‡‡	246 (183–329)§	157 (105–235)**
Insulin sensitivity							
ISI (μmol · kg LBM^{-1} · min^{-1} · pmol^{-1} · l^{-1})	0.237 ± 0.008	0.206 ± 0.014	0.164 ± 0.028††	0.104	0.206 ± 0.034	0.117 ± 0.014$§	0.161 ± 0.021&**

Data for insulin secretion are geometric means (95% CI). Data for insulin sensitivity is mean ± SEM. ANOVA was used with gender, age, BMI, and WHR as covariates. NFG/NGT versus NFG/IGT: *$P < 0.001$; NFG/IGT versus NFG/DGT: †$P = 0.054$, ††$P = 0.023$, †††$P = 0.002$; NFG/IGT versus IFG/IGT: #$P = 0.02$; NFG/NGT versus NFG/DGT: ¶$P < 0.001$; NFG/NGT versus type 2; **$P < 0.01$; NFG/NGT versus IFG/IGT: ‡‡$P < 0.001$; IFG/IGT versus type 2: &$P < 0.05$; NFG/NGT versus IFG/DGT: §$P < 0.002$; IFG/IGT versus IFG/DGT: $$P = 0.024$.

TABLE 3
First- and second-phase insulin secretion and insulin sensitivity in subjects with normal fasting glucose (NFG), impaired fasting glucose (IFG), and type 2 diabetes, subdivided as in Tables 1 and 2, expressed as percentage of expected with adjustment for age, gender, BMI, and WHR. Multiple linear regression was performed on data of NFG/NGT subjects for the assessment of the adjustment for age, gender, BMI, and WHR.

	NFG		IFG			
Fasting glycemia	NFG/IGT	NFG/DGT	IFG/NGT	IFG/IGT	IFG/DGT	Type 2 diabetes
n	86	10	2	9	13	15
Insulin secretion						
First phase (%)	84 ± 5	42 ± 6	114	52 ± 9	59 ± 9	59 ± 16
Second phase (%)	83 ± 5	54 ± 8	132	66 ± 9	72 ± 9	63 ± 13
Insulin sensitivity						
ISI (%)	95 ± 6	68 ± 9	51	95 ± 14	58 ± 8	68 ± 9

Data are mean ± SEM, expressed as percentage of expected.

groups, regardless of inclusion of the above covariates (all $P > 0.25$).

Tissue insulin sensitivity. ISI was lower in IFG/DGT versus IFG/IGT, regardless of inclusion of covariates (both $P < 0.03$).

Comparison between IFG subgroups and NFG subgroups

β-Cell function. First-phase secretion was not statistically significantly lower in IFG/IGT than in NFG/IGT ($P = 0.058$); the difference became significant when gender, age, BMI, and WHR ($P = 0.02$) or ISI ($P = 0.009$) were taken as covariates. Second-phase secretion was not significantly different between NFG/IGT and IFG/IGT ($P > 0.10$), regardless of the inclusion of the above covariates. First- and second-phase secretion were not significantly different between NFG/DGT and IFG/DGT, regardless of the inclusion of the above covariates (all $P > 0.05$).

Tissue insulin sensitivity. ISI values in NFG/IGT and IFG/IGT were indistinguishable ($P = 0.99$), regardless of covariates ($P = 0.43$). ISI values in NFG/DGT and IFG/DGT were also not statistically significantly different ($P = 0.14$), regardless of covariates ($P = 0.058$).

Type 2 diabetes (fasting hyperglycemia)

β-Cell function. Both the first and second phases of insulin secretion were lower in type 2 diabetes than in NFG/NGT and NFG/IGT, both with and without inclusion of covariates (all $P < 0.02$), while no statistical differences were found between the other groups and type 2 diabetes (all $P > 0.10$).

Tissue insulin sensitivity. ISI was lower in type 2 diabetes than in NFG/NGT, regardless of inclusion of covariates (all $P < 0.02$), while no differences were seen with the other groups (all $P > 0.10$).

Multiple linear regression. In NFG/NGT subjects, multiple linear regression of first- and second-phase secretion data (after log-transformation) and of ISI data with gender, age, BMI, and WHR showed significant relationships:

Log (first phase): $2.299 - 0.0302 \times \text{gender} - 0.000134 \times \text{age} + 0.018 \times \text{BMI} + 0.242 \times \text{WHR}$ ($P < 0.001$)

Log (second phase): $1.770 - 0.0310 \times \text{gender} - 0.00113 \times \text{age} + 0.0168 \times \text{BMI} + 0.436 \times \text{WHR}$ ($P < 0.001$)

ISI: $0.58 + 0.00924 \times \text{gender} + 0.000045 \times \text{age} - 0.00911 \times \text{BMI} - 0.137 \times \text{WHR}$ ($P < 0.001$).

In the other six groups, predicted values for first- and second-phase secretion and ISI were calculated. The actual measured parameters were divided by the predicted values, and expressed as percentage of predicted in order to assess the disturbances in β-cell function and ISI (Table 3).

DISCUSSION

It is often assumed that the transition from NFG to IFG, and then to frank (fasting) hyperglycemia develops in a specific order, in which insulin resistance precedes deterioration in β-cell function. The current studies are cross-sectional studies of β-cell function and tissue insulin sensitivity in subjects with a wide range of disturbances in glucose homeostasis. We have divided the subjects into subgroups according to fasting glycemia (NFG, IFG, and frank hyperglycemia or type 2 diabetes) and according to 2-h OGTT findings (NGT, IGT, and DGT). Since overweight not only affects insulin sensitivity, but can also lead to an adaptation of the pancreatic β-cell function, we have taken measures of overweight into account (13,14).

These studies show disturbances in β-cell function in subjects with IFG and with type 2 diabetes. Further subdivision according to the OGTT led to several findings. Even in subjects with NFG, the occurrence of IGT was already associated with a disturbed β-cell function, while the decline in ISI was mainly related to overweight. In NFG subjects with a postglucose hyperglycemia (in the diabetic range), the decrease in tissue insulin sensitivity could not be explained by overweight.

One striking observation is that only 2 subjects (of 319 subjects) showed NGT in spite of IFG. In view of the fact that a much larger group (86 subjects) has the inverse (NFG and IGT), it appears reasonable to propose that impairment of glucose tolerance will generally precede an elevation in fasting glycemia. Since the NFG/IGT subjects have a clearly lower β-cell function than the control group (NFG/NGT), it now becomes apparent that deterioration in β-cell function is a very early phenomenon to be observed in subjects with deterioration in glucose homeostasis. This has also been found in previous reports from our group and from others (2–8,15–17). At the same time, these subjects were obese and showed a diminished tissue insulin sensitivity compared with control subjects (NFG/NGT), as previously reported from studies in other IGT subjects (18). However, since ANOVA showed that the difference in tissue insulin sensitivity disappeared when gender, age, BMI, and WHR were used, it follows that the

difference in tissue insulin sensitivity was related to these factors (presumably overweight) and not to another (inherent or genetically transmitted) "insulin resistance" factor. Indeed, overweight itself is well known to lead to (potentially reversible) insulin resistance, presumably via the release of adipocyte-derived substances; free fatty acids, tumor necrosis factor-α, and most recently resistin have been suggested to be such substances (19–22).

The present studies in IFG subjects with IGT indicate that, in comparison to their NFG counterparts (NFG/IGT), their β-cell function (first-phase insulin release) is further diminished, while no deterioration in tissue insulin sensitivity is observed. Only in subjects with more postglucose load hyperglycemia in the diabetic range (IFG/DGT) was a marked decline in tissue insulin sensitivity observed. This suggests that deterioration in insulin sensitivity occurs fairly late in the development of type 2 diabetes mellitus, and that it appears to be preceded by disturbances in β-cell function.

Finally, we included a number of subjects with frank fasting hyperglycemia in the diabetic range (i.e., $>$ 7.0 mmol/l). These subjects show both a decreased β-cell function as compared to normal control subjects, and lower tissue insulin sensitivity as compared to both normal control subjects and IFG/IGT subjects. It is of note that, in the type 2 diabetic subjects, the lower insulin sensitivity does not appear to be related to being overweight. This would imply that it is a specific phenomenon of genetic origin in these subjects or it is possibly related to their hyperglycemia, or both. Indeed, there is ample evidence that hyperglycemia itself may induce insulin resistance, which is (partly) reversible, in both type 1 diabetes (honeymoon phase) and type 2 diabetes (23,24).

Multiple linear regression indicated the influence of gender, age, BMI, and WHR for β-cell function and insulin sensitivity in subjects with NFG and NGT (8). In an attempt to show the disturbances in β-cell function and insulin sensitivity, the "predicted" values for these parameters were calculated for the six groups with disturbances in glucose homeostasis, adjusting for gender, age, BMI, and WHR. However, the accuracy of each of the adjustments is limited due to the (limited) variability in each of the parameters (age, BMI, and WHR) in the reference group. Therefore, extrapolation to subgroups with appreciably older age or larger (or smaller) BMI and/or larger WHR is hazardous, and the precision of the "predicted" values is at best uncertain.

In conclusion, early stages of disturbances in glucose homeostasis are associated with disturbances in β-cell function, while later stages are associated with (further) disturbances in insulin sensitivity. In subjects with NFG, IGT is associated with disturbances in β-cell function, while the decrease in tissue insulin sensitivity appears to be related to being overweight. In IFG, β-cell function is generally disturbed. In subjects with DGT, a decrease in insulin sensitivity is seen in subjects with NFG and in those with IFG.

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