Contribution of Insulin-Stimulated Glucose Uptake and Basal Hepatic Insulin Sensitivity to Surrogate Measures of Insulin Sensitivity

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OBJECTIVE — The goal of this study was to evaluate the performance of surrogate measures of insulin sensitivity and insulin secretion.

RESEARCH DESIGN AND METHODS — The homeostasis model assessment (HOMA) of insulin resistance (IR) and the insulin sensitivity index (S_i) from oral glucose tolerance test (OGTT) were compared with the *M* value from a hyperinsulinemic-euglycemic clamp in 467 subjects with various degrees of glucose tolerance. Endogenous glucose production (EGP) and hepatic insulin sensitivity were determined in a subset ($n = 143$). Insulin secretion was estimated as the HOMA β-cell index and as the insulinogenic index from the first 30 min of the OGTT (I/G30) and compared with the first-phase insulin response (FPIR) to an intravenous glucose tolerance test ($n = 218$).

RESULTS — The *M* value correlated with the HOMA-IR ($r = -0.591$, $P < 0.0001$) and the S_i ($r = 0.533$, $P < 0.0001$) indexes in the total study group. HOMA-IR correlated with basal EGP in the total study group ($r = 0.378$, $P < 0.0005$) and in subjects with diabetes ($r = 0.330$, $P = 0.01$). However, neither HOMA-IR nor S_i correlated significantly with the *M* value in subjects with impaired fasting glucose (IFG) ($r = -0.108$, $P = 0.5$; $r = 0.01$, $P = 0.9$) or IFG/impaired glucose tolerance (IGT) ($r = -0.167$, $P = 0.4$; $r = 0.09$, $P = 0.6$). The HOMA-IR correlated with hepatic insulin sensitivity in the whole study group ($r = -0.395$, $P < 0.005$) as well as in the IFG/IGT subgroup ($r = -0.634$, $P = 0.002$) and in the diabetic subgroup ($r = -0.348$, $P = 0.008$). In subjects with IFG/IGT, hepatic insulin sensitivity was the most important determinant of HOMA-IR, explaining 40% of its variation. The HOMA β-cell index showed a weak correlation with FPIR in the whole study group ($r = 0.294$, $P = 0.001$) but not in the subgroups. In contrast, the I/G30 correlated with FPIR in the whole study group ($r = 0.472$, $P < 0.0005$) and in the IFG/IGT subgroup ($r = 0.493$, $P < 0.005$).

CONCLUSIONS — HOMA-IR is dependent upon both peripheral and hepatic insulin sensitivity, the contribution of which differs between subjects with normal and elevated fasting glucose concentrations. These discrepancies develop as a consequence of a nonparallel deterioration of the variables included in the equations with worsening of glucose tolerance.

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Abbreviations: EGP, endogenous glucose production; FPIR, first-phase insulin response; HOMA, homeostasis model assessment; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; IVGTT, intravenous glucose tolerance test; I/G30, insulinogenic index from the first 30 min of the OGTT; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

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

Both insulin resistance and impaired β-cell function contribute to the chronic hyperglycemia in type 2 diabetes. Whereas insulin resistance is present several years before the manifestation of diabetes, impaired β-cell function is usually not seen until glucose tolerance becomes impaired (1–4). The study of the relative contribution of impaired β-cell function and insulin resistance to the development of glucose intolerance and diabetes requires reliable assessment methods. The hyperinsulinemic-euglycemic clamp and the hyperglycemic clamp or the intravenous glucose tolerance test (IVGTT) (5–8) are considered the gold standards for the assessment of insulin sensitivity and insulin secretion; but these tests are laborious, and more simple tests are required for epidemiological studies. The homeostasis model assessment (HOMA) insulin resistance (IR) index estimates insulin sensitivity from fasting insulin and glucose concentrations, whereas the insulin sensitivity index (S_i) estimates insulin sensitivity from insulin and glucose response during an oral glucose tolerance test (OGTT) (9–11). In several studies, these tests have shown a good correlation with the *M* value obtained during the euglycemic clamp (9–17). Insulin secretion can be estimated by the HOMA β-cell index from fasting insulin or C-peptide and glucose concentrations (9), whereas the insulinogenic index uses the increment above basal in insulin and glucose concentrations during the first 30 min of the OGTT (I/G30) (18). These tests have shown reasonable correlations with measures obtained during a hyperglycemic clamp (7,8).

However, most earlier studies were restricted to subjects with either normal glucose tolerance (NGT) or diabetes (9,10,12). Recently, a new pre-diabetic stage of glucose tolerance, impaired fasting glucose (IFG), has been introduced in addition to impaired glucose tolerance

(IGT) (19). Reliable estimates of insulin sensitivity and insulin secretion are particularly needed in these pre-diabetic stages, but it is not known whether the surrogate measures are appropriate for use in this population.

The aim of the study was to compare surrogate estimates of insulin sensitivity and insulin secretion with measures of whole body and hepatic insulin sensitivity obtained from the euglycemic clamp and measures of insulin secretion obtained from IVGTT in subjects with various degrees of glucose tolerance including IFG and IGT.

RESEARCH DESIGN AND METHODS

— Subjects for the present study were part of the Botnia study (20) and the Malmö Prospective study (21,22). The Botnia study was started in 1990 on the West coast of Finland to identify genetic and metabolic factors contributing to the pathogenesis of type 2 diabetes (20). The Malmö Prospective study was started in 1974 as an intervention project to prevent type 2 diabetes in men born between 1926 and 1935 (22,23).

Subjects with various degrees of glucose tolerance were randomly chosen from the study population to participate in a euglycemic clamp, OGTT, and IVGTT. Informed consent was obtained from all subjects, and the studies were approved by the local ethics committees. Subjects were classified into different stages of glucose tolerance according to the revised World Health Organization criteria (19). Thus, 467 subjects (216 with NGT, 106 with IFG and/or IGT, and 145 with type 2 diabetes) participated in a euglycemic clamp and an OGTT. Of the 106 subjects with IFG/IGT, 31 had isolated IFG (fasting plasma glucose 6.1–6.9 mmol/l), 46 had isolated IGT (2-h glucose value 7.8–11.0 mmol/l), and 29 had both IFG and IGT. For estimation of endogenous glucose production (EGP) rates, a euglycemic clamp combined with [3-^{3}H]glucose infusion was performed in a subset of 143 subjects (54 with NGT, 30 with IFG/IGT, 59 with type 2 diabetes). An IVGTT was also performed for 218 subjects (132 with NGT, 50 with IFG/IGT, and 36 with type 2 diabetes).

All subjects participated in an OGTT by ingesting 75 g of glucose in a volume of 300 ml (Glucodyn; Leiras, Turku, Finland) after a 12-h overnight fast. Samples for the measurement of glucose and insulin were drawn at −10, 0, 30, 60, and 120 min. Indexes of insulin sensitivity and insulin secretion were calculated from the OGTT. The HOMA-IR index was calculated using the fasting plasma glucose and insulin concentration ([fasting glucose {mmol/l} × fasting insulin {μU/ml}]/22.5) (9).

The S_i from OGTT was calculated as follows (10).

$$\frac{10{,}000}{\sqrt{([\text{FPG} \times \text{fasting insulin}] \times [\text{mean glucose} \times \text{mean insulin during OGTT}])}}$$

All subjects underwent a hyperinsulinemic-euglycemic clamp (5). The EGP rate was determined in a subset with a hyperinsulinemic-euglycemic clamp combined with intravenous infusion of [3-^{3}H]glucose (Amersham International, Little Chalfont, U.K.). At the start of this infusion, a priming dose of [3-^{3}H]glucose (8.3 μCi/m^2) was given and followed by a constant (0.083 $\mu Ci \cdot m^{-2} \cdot min^{-1}$) infusion throughout the clamp. Blood samples were collected at timed intervals in fluoride-treated tubes for the determination of plasma glucose and plasma [3-^{3}H]glucose-specific activity. After a 150-min tracer equilibration period, a bolus dose of insulin (Actrapid Human, 100 U/ml; Novo Nordisk, Gentofte, Denmark) was administered intravenously followed by a constant infusion of insulin at a rate of 45 mU/m^2 and continued for 120 min. A variable infusion of 20% glucose was started to maintain plasma glucose concentration unchanged at 5.5 mmol/l for 120 min. The mean coefficient of variation (CV) for glucose values during clamp was 6.3%. Plasma glucose was measured at 5-min intervals throughout the clamp. Insulin sensitivity (*M* value) was calculated from the glucose infusion rates during the last 60 min of the euglycemic clamp. Basal EGP was calculated by dividing the [3-^{3}H]glucose infusion rate by the steady state plateau of glucose-specific activity in plasma during the last 30 min of the basal tracer infusion period. Because the EGP is extremely sensitive to the fasting insulin concentrations (24,25), we determined the hepatic insulin sensitivity by dividing the basal EGP rates by the fasting insulin concentration (25).

In the IVGTT, 0.3 g glucose/kg body wt of a 50% glucose solution was given at time 0. Blood samples for the measurement of serum insulin and glucose were obtained at −10, 0, 2, 4, 6, 8, 10, 20, 40, 50, 60, 120, and 180 min. The incremental area during the first 10 min of the test was determined by the trapezoidal method and was called first-phase insulin response (FPIR). β-Cell function was also estimated as the HOMA β-cell index, ([fasting insulin {μU/ml} × 20]/[fasting glucose {mmol/l} − 3.5]) (9), and as the I/G30 during the first 30 min of the OGTT (insulin 30 min − insulin 0 min/glucose 30 min − glucose 0 min) (18).

Plasma glucose was measured with a glucose oxidation method, using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Serum insulin concentrations were measured with radioimmunoassay (Pharmacia, Uppsala, Sweden) with an interassay CV of 5%. [3-^{3}H]Glucose-specific activity was measured in duplicate from the supernatant of 0.5 mol/l perchloric acid extract of samples after evaporation of radiolabeled water. Fat-free mass was measured with infrared spectroscopy from the outer layer of the biceps on the dominant arm using a Futrex 5000 device (Futrex, Gaithersburg, MD). The CV of repeated measures by the same investigator was <1%, and this method correlates well with the fat-free mass obtained by bioelectric impedance method (26).

Statistical analysis

Data are expressed as means ± SE. Data for insulin and HOMA were logarithmically transformed for normality. The significance of difference between the three groups was tested by the Mann-Whitney *U* test. The relationship between the different estimates of insulin sensitivity and insulin secretion were determined using the Pearson's correlation coefficient. Comparison of insulin sensitivity between different stages of glucose tolerance was performed after adjusting for the difference in age, sex, and BMI among the groups. Statistical analyses were carried out using the NCSS statistical software (Number Cruncher Statistical System, Cork, Ireland).

RESULTS

— Table 1 shows the clinical characteristics of the three groups. After

Table 1—*Clinical characteristics of subjects in relation to glucose tolerance*

	NGT	IFG	IGT	IFG/IGT	Type 2 diabetes
n (men/women)	216 (134/82)	31 (22/9)	46 (33/13)	29 (25/4)	146 (120/25)
Age (years)	50.3 ± 15.2	51.3 ± 15.1	60.6 ± 10.9*†	62.9 ± 9.7*†	61.6 ± 10.6*†
BMI (kg/m^2)	25.8 ± 3.9	27.2 ± 3.7	27.2 ± 3.5	27.8 ± 3.9	27.9 ± 4.5†
Lean body mass (kg)	57.2 ± 9.9	59.8 ± 11.2	59.5 ± 9.7	61.9 ± 9.5	61.6 ± 9.6†
Waist-to-hip ratio (men)*	0.95 ± 0.06	0.96 ± 0.05	0.96 ± 0.04	0.98 ± 0.05†	0.987 ± 0.05†
Waist-to-hip ratio (women)	0.84 ± 0.06	0.85 ± 0.07	0.84 ± 0.04	0.85 ± 0.03	0.86 ± 0.05
Fasting plasma glucose (mmol/l)	5.37 ± 0.4	6.4 ± 0.2†	5.5 ± 0.4	6.4 ± 0.2†	9.8 ± 3.5†‡
2-h glucose (mmol/l)	5.93 ± 1.1	6.34 ± 1.1†	8.8 ± 0.7†	9.2 ± 0.9†	15.2 ± 4.9*†‡
HbA_{1c} (%)	5.4 ± 0.5	5.36 ± 0.5	5.58 ± 0.6	5.86 ± 0.6	7.4 ± 1.9*†‡
M value (mg · ffmkg^{-1} · min^{-1})§	8.41 ± 3.3	7.76 ± 3.3	6.82 ± 2.6†	5.86 ± 2.4*†	5.33 ± 2.4*†
lnHOMA-IR§	0.49 ± 0.5	0.87 ± 0.4†	0.86 ± 0.5†	1.18 ± 0.6†	1.52 ± 0.7*†‡
S_i from OGTT§	7.0 ± 3.9	4.6 ± 1.6†	4.39 ± 2.05†	3.9 ± 2.1†	4.09 ± 2.7†
EGP (mg · kg FFM^{-1} · min^{-1}) (*n*)	2.74 ± 0.4 (54)		2.73 ± 0.3 (30)		3.28 ± 0.9 (59)†‡
Hepatic insulin sensitivity (mg · kg FFM^{-1} · min^{-1} · mUl^{-1})	0.87 ± 0.9		0.73 ± 0.7		0.50 ± 0.35†

Data are means ± SD. *$P < 0.05$ vs. IFG; †$P < 0.05$ vs. NGT; ‡$P < 0.05$ vs. IFG/IGT. §Values adjusted for difference in age, BMI, and sex. FFM, fat-free mass.

adjustment for age and sex, subjects with IFG and/or IGT and diabetes had higher BMI and lean body mass compared with NGT subjects. The overall prevalence of obesity defined as BMI >27 kg/m^2 was 37% in subjects with NGT, 50% in subjects with IFG/IGT, and 60% in subjects with diabetes.

Insulin sensitivity

The *M* value was inversely correlated with both the fasting ($r = -0.387$, $P < 0.0005$) and the 2-h ($r = -0.494$, $P < 0.0005$) plasma glucose concentrations Consequently, the *M* value showed a progressive decline with worsening of glucose tolerance (Fig. 1). Subjects with IFG/IGT had 19% ($P < 0.05$) and patients with type 2 diabetes had 38% ($P < 0.005$) lower *M* values than subjects with NGT.

Although the HOMA-IR ($r = -0.591$, $P < 0.005$) correlated with the *M* value in the total study group and in subjects with NGT ($r = 0.364$, $P < 0.0005$), no significant correlation was seen in subjects with either IFG alone ($r = -0.108$, $P = 0.5$) or IFG/IGT ($r = -0.167$, $P = 0.4$) (Table 2). The same applied to S_i, which correlated with the *M* value in the whole study group ($r = 0.533$, $P < 0.0001$) but not in subjects with IFG ($r = 0.01$, $P = 0.9$) or IFG/IGT ($r = 0.09$, $P = 0.6$). However, in subjects with diabetes, both HOMA-IR ($r = -0.525$, $P < 0.0005$) and S_i ($r = 0.441$, $P < 0.0005$) correlated with the *M* value.

The HOMA-IR correlated with the basal EGP in the whole study group ($r = 0.368$, $P < 0.0005$) and in subjects with diabetes ($r = 0.275$, $P = 0.04$), although no such relationship was observed in the NGT and IFG/IGT subgroups. On the other hand, HOMA-IR correlated with hepatic insulin sensitivity in the total study group ($r = -0.395$, $P < 0.005$), as well as in the IFG/IGT ($r = -0.634$, $P = 0.002$) and in the diabetic subgroups ($r = -0.348$, $P = 0.008$). Similarly, the S_i cor-

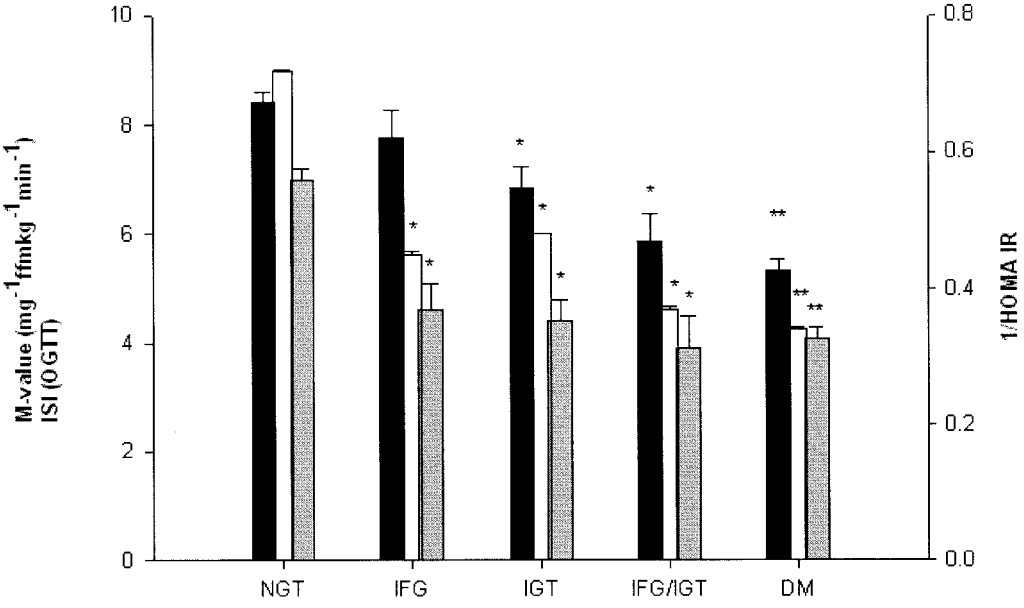

Figure 1—*Insulin sensitivity measured by the hyperinsulinemic-euglycemic clamp* (■) *or S_i from OGTT* (▨) *or 1/HOMA-IR* (□) *reciprocal of HOMA-IR used for similar graphical representation in subjects with NGT, IFG, IGT, IFG/IGT, and type 2 diabetes (DM). *P < 0.05 vs. NGT; **P < 0.005 vs. NGT.*

Table 2—*Correlation coefficients between surrogate measures of insulin sensitivity and the* M *value from a euglycemic clamp and measures of insulin secretion from OGTT and the FPIR from the IVGTT*

	All	NGT	IFG	IGT	IFG/IGT	Type 2 diabetes
M value						
n	467	216	31	46	29	145
lnHOMA	−0.591 (<0.0001)	−0.364 (<0.0005)	−0.108 (0.5)	−0.407 (0.004)	−0.167 (0.4)	−0.525 (<0.0005)
S_i	0.533 (<0.0001)	0.338 (<0.0005)	0.01 (0.9)	0.394 (0.007)	0.09 (0.6)	0.441 (<0.0005)
FPIR						
n	218	132	—	50	—	36
HOMA B-cell index	0.294 (<0.005)	0.135 (0.04)	—	0.173 (0.2)	—	0.305 (0.19)
Insulinogenic index (I/G30)	0.472 (<0.0005)	0.233 (0.009)	—	0.493 (<0.005)	—	0.352 (0.05)

Values within parentheses represent the *P* value.

related with hepatic insulin sensitivity in the whole group ($r = 0.427$, $P < 0.0005$) as well as in the IFG/IGT ($r = 0.769$, $P < 0.0005$) and diabetic subgroups ($r = 0.422$, $P = 0.001$).

A stepwise multiple regression analysis, using HOMA-IR and S_i as the dependent variables and whole body glucose uptake (*M* value) and hepatic insulin sensitivity as independent variables (Table 3), showed that the *M* value explained 34% of the variation in the HOMA-IR in the whole group, whereas hepatic insulin sensitivity did not significantly contribute to it. However, in subjects with IFG/IGT, hepatic insulin sensitivity explained 40% of the variability in the HOMA-IR and 59% of the variability in the S_i, whereas whole body glucose uptake accounted for only 10% of the variation in HOMA-IR and did not significantly contribute to S_i.

Insulin secretion

The FPIR from IVGTT declined progressively with worsening of glucose tolerance (Fig. 2). The FPIR ($r = -0.447$, $P < 0.005$) correlated negatively with both fasting and 2-h glucose concentrations during the OGTT. The FPIR in the IFG/IGT subjects was slightly lower than in the NGT subjects (266 ± 15 vs. 218.7 ± 23 mIU/l, NS), but subjects with diabetes had a markedly lower FPIR compared with the NGT subjects (266 ± 15 vs. 38.8 ± 27 mIU/l, $P < 0.05$) (Fig. 2). Also, the I/G30 declined progressively with worsening of glucose tolerance and correlated with the fasting ($r = -0.357$, $P < 0.0005$) and 2-h ($r = -0.409$, $P <$

Table 3—*Stepwise multiple regression analysis in the total study group and subgroups using lnHOMA-IR and* S_i *as the dependent variables and hepatic insulin sensitivity and M value as the independent variables*

		lnHOMA-IR		S_i	
	n	Partial correlation coefficient	Final model increase in multiple r^2	Partial correlation coefficient	Final model increase in multiple r^2
Total study group	143				
Hepatic insulin sensitivity (mg · kg FFM^{-1} · min^{-1} · mUl^{-1})		−0.168	NS	0.229†	0.037
M value (mg · ffmkg^{-1} · min^{-1})		−0.588*	0.341	0.436*	0.300
Multiple r^2			0.341*		0.337*
NGT	54				
Hepatic insulin sensitivity (mg · kg FFM^{-1} · min^{-1} · mUl^{-1})		−0.166	NS	0.174	NS
M value (mg · kg FFM^{-1} · min^{-1})		−0.369*	0.136	0.442*	0.195
Multiple r^2			0.136†		0.195*
IFG/IGT	30				
Hepatic insulin sensitivity (mg · kg FFM^{-1} · min^{-1} · mUl^{-1})		−0.572*	0.402	0.769*	0.591
M value (mg · kg FFM^{-1} · min^{-1})		−0.425†	0.108	0.366	NS
Multiple r^2			0.510*		0.591*
Type 2 diabetes	59				
Hepatic insulin sensitivity (mg · kg FFM^{-1} · min^{-1} · mUl^{-1})		−0.062	NS	0.422†	0.178
M value (mg · kg FFM^{-1} · min^{-1})		−0.480*	0.230	0.196	NS
Multiple r^2			0.230*	0.178†	

Variables included in the multiple regression analysis and their respective contribution to the value of multiple r^2. *$P < 0.001$; †$P < 0.05$. FFM, fat-free mass.

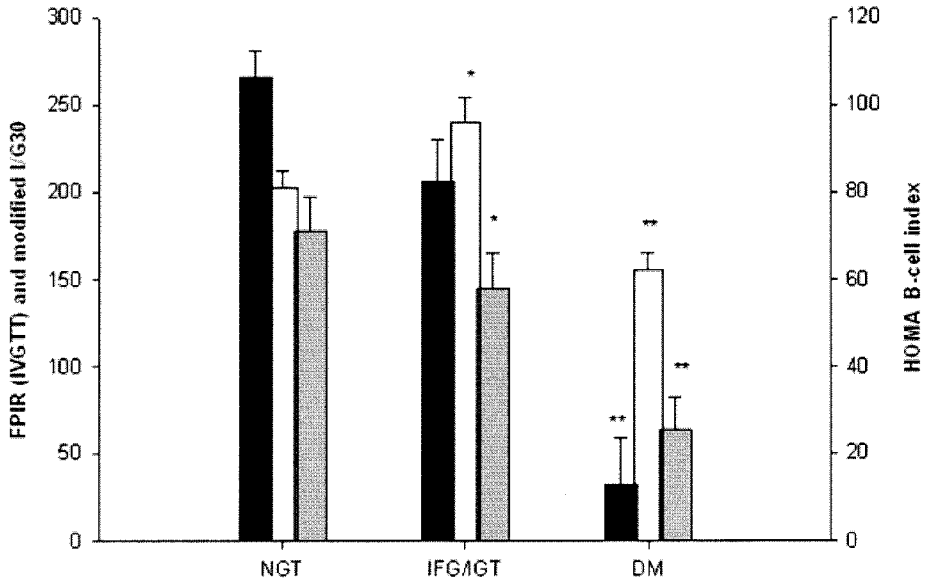

Figure 2—*Insulin secretion measured as FPIR during IVGTT (■), HOMA β-cell index (□), and I/G30 (▨) in subjects with NGT, IFG/IGT, and type 2 diabetes (DM). The I/G30 values have been modified ([I/G30] ×10) for the same graphical representation as FPIR.* *P < *0.05 vs. NGT;* **P < *0.005 vs. NGT.*

0.0005) plasma glucose concentrations. The HOMA β-cell index gave a different picture with a trend toward enhanced insulin secretion in subjects with IFG/IGT compared with NGT. Whereas the HOMA β-cell index correlated with FPIR only in the whole study group ($r = 0.294$, $P < 0.005$) (Table 2), the I/G30 correlated with FPIR in the whole group ($r = 0.472$, $P < 0.0005$) as well as in the NGT ($r = 0.233$, $P = 0.009$), IFG/IGT ($r = 0.403$, $P = 0.006$), and type 2 diabetic ($r = 0.352$, $P = 0.05$) groups.

CONCLUSIONS — The convenience of the surrogate markers makes their use attractive in epidemiological studies assessing the role of disturbances in insulin sensitivity and β-cell function for the development of abnormal glucose tolerance. However, this requires that the markers accurately reflect these disturbances across different groups with intermediate glucose tolerance. In subjects with IFG and IFG/IGT, the HOMA-IR obtained at the fasting state and the S_i obtained from OGTT did not correlate with the *M* value, which is regarded as the gold standard for whole body insulin sensitivity, whereas they correlated with hepatic insulin sensitivity. Concerning insulin secretion, we could not see any correlation between the HOMA β-cell index and the FPIR estimated from an IVGTT. In contrast, the I/G30 obtained from OGTT performed fairly well, showing a correlation with FPIR not only in all subjects but also in the subgroup with IFG/IGT.

HOMA

When first developed by Matthews et al. (9), the HOMA-IR was shown to correlate strongly with the *M* value in both nondiabetic and diabetic subjects ($r = 0.83$ and $r = 0.92$, respectively). Similar, although weaker, correlations have been reported by other authors (27,28). Our results differ from those by Bonora et al. (13) who recently reported a strong correlation between the HOMA-IR and the *M* value in both nondiabetic ($r = -0.754$, $P < 005$, $n = 62$) and diabetic ($r = -0.695$, $P < 0.005$, $n = 53$) subjects. However, the number of IFG/IGT subjects included in their nondiabetic group was not given, and a separate analysis in that subgroup was not performed. Another potential explanation for the difference could be that Bonora et al. (13) used a lower dose of insulin infusion during the clamp (20 vs. 45 mU/m^2 in the present study), which may better reflect the insulin values seen in the fasting state and thus the HOMA estimates. Supporting our observations, a recent study in elderly subjects with IGT also demonstrated that the HOMA-IR did not accurately predict insulin sensitivity (27).

HOMA-IR is based upon the correlation between insulin and glucose values and the assumption that rising glucose concentrations lead to a compensatory increase in insulin concentrations. Although a linear relationship is observed between fasting glucose and insulin concentrations in subjects with NGT ($r = 0.232$, $P = 0.002$), this correlation is not seen in subjects with IFG ($r = 0.09$, NS). Therefore, in subjects with abnormalities in fasting glucose concentrations, the HOMA-IR index may be erroneous.

From the direct comparison of HOMA-IR and the *M* value in the present study (Fig. 1), it is apparent that the HOMA-IR seems to be influenced more by the fasting glucose concentration than the insulin sensitivity per se. The impairment of insulin sensitivity by HOMA-IR in subjects with IFG/IGT and diabetes appeared to be greater when assessed by HOMA method than when assessed by the euglycemic clamp. Because fasting glucose concentrations reflect basal hepatic glucose production, we also evaluated the possibility whether the HOMA-IR is more related to hepatic insulin sensitivity than to peripheral glucose uptake, which mostly measures skeletal muscle glucose uptake. In fact, a significant relationship was observed between hepatic insulin sensitivity and the HOMA-IR regardless of the stage of glucose tolerance. Furthermore, in subjects with IFG/IGT, the hepatic insulin sensitivity accounted for most of the variation in the HOMA-IR, suggesting that in subjects with minimal elevation of fasting plasma glucose, these indexes are dependent upon hepatic rather than peripheral insulin sensitivity.

S_i from OGTT

This index derived from the OGTT is supposed to take into account both peripheral and hepatic insulin sensitivity. In the

original publication by Matsuda and DeFronzo (10), it showed a strong correlation with the *M* value. Again, we observed a much weaker correlation in subjects with NGT than that reported in the original study, whereas there was no significant correlation in subjects with IFG and IGT. As our OGTT did not include a 90-min sample, our data are not completely comparable with the data by Matsuda and DeFronzo (10). Although S_i was slightly better than HOMA, it cannot be regarded good enough for the estimation of insulin sensitivity in subjects with IFG/IGT. On the other hand, S_i has been shown to predict future diabetes better than HOMA (29).

Surrogate measures of β-cell function

Although there are no gold standards for the estimation of insulin secretion, the hyperglycemic clamp provides estimates of insulin secretion during steady state conditions of glucose. However, as the steady state is not achieved during the first 10 min, the estimates of the early phase of insulin secretion are very similar during the first 10 min of the hyperglycemic clamp and the IVGTT. Therefore, we used the FPIR estimated during the IVGTT as the reference value for insulin secretion. This can be justified because a low FPIR has been shown to predict progression toward type 2 diabetes (30). The I/G30 obtained from OGTT correlated well with FPIR in all subjects, including the IFG/IGT subgroup, whereas the HOMA β-cell index did not correlate with FPIR in subjects with IFG/IGT or in subjects with type 2 diabetes. This again suggests that the HOMA β-cell index is influenced more by the fasting plasma glucose concentrations than by the insulin secretion. In subjects with NGT, the fasting insulin concentrations may be low despite high poststimulatory values and high FPIR. Likewise, in some subjects with IGT or diabetes, the fasting insulin concentrations may be high, although the FPIR will be low. Another problem is that the relationship between the fasting glucose and insulin is not linear, nor does it change in parallel with worsening of glucose tolerance. Consequently, even though the fasting glucose concentrations are taken into account, it is not always possible to estimate the insulin secretion accurately from this index.

Although this study (to our knowledge) is the largest with data on different estimates of insulin sensitivity and insulin secretion in individuals with IFG/IGT, the groups were still relatively small, which may influence the interpretation of the results. In conclusion, simple estimates of insulin sensitivity (HOMA-IR, S_i) do not accurately describe changes in whole body glucose uptake in subjects with IFG and IGT. The HOMA-IR is dependent upon both peripheral and hepatic insulin sensitivity, the contribution of which differs between subjects with normal and elevated fasting glucose concentrations. Of surrogate estimates of insulin secretion, the I/G30 represents an acceptable measure of insulin secretion irrespective of the degree of glucose tolerance.

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