Use of the Oral Glucose Tolerance Test to Assess Insulin Release and Insulin Sensitivity

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OBJECTIVE — The oral glucose tolerance test (OGTT) has often been used to evaluate apparent insulin release and insulin resistance in various clinical settings. However, because insulin sensitivity and insulin release are interdependent, to what extent they can be predicted from an OGTT is unclear.

RESEARCH DESIGN AND METHODS — We studied insulin sensitivity using the euglycemic-hyperinsulinemic clamp and insulin release using the hyperglycemic clamp in 104 nondiabetic volunteers who had also undergone an OGTT. Demographic parameters (BMI, waist-to-hip ratio, age) and plasma glucose and insulin values from the OGTT were subjected to multiple linear regression to predict the metabolic clearance rate (MCR) of glucose, the insulin sensitivity index (ISI), and first-phase (1st PH) and second-phase (2nd PH) insulin release as measured with the respective clamps.

RESULTS — The equations predicting MCR and ISI contained BMI, insulin (120 min), and glucose (90 min) and were highly correlated with the measured MCR ($r = 0.80$, $P < 0.00005$) and ISI ($r = 0.79$, $P < 0.00005$). The equations predicting 1st PH and 2nd PH contained insulin (0 and 30 min) and glucose (30 min) and were also highly correlated with the measured 1st PH ($r = 0.78$, $P < 0.00005$) and 2nd PH ($r = 0.79$, $P < 0.00005$). The parameters predicted by our equations correlated better with the measured parameters than homeostasis model assessment for secretion and resistance, the Δ30-min insulin/Δ30-min glucose ratio for secretion and insulin (120 min) for insulin resistance taken from the OGTT.

CONCLUSIONS — We thus conclude that predicting insulin sensitivity and insulin release with reasonable accuracy from simple demographic parameters and values obtained during an OGTT is possible. The derived equations should be used in various clinical settings in which the use of clamps or the minimal model would be impractical.

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Abbreviations: AUC, area under the curve; 1st PH, first-phase insulin release; Gluc, plasma glucose concentration during the OGTT; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; Ins, plasma insulin concentration during the OGTT; IR, insulin resistance index; ISI, insulin sensitivity index; ISI(comp), composite insulin sensitivity index; MCR, metabolic clearance rate; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; 2nd PH, second-phase insulin release; Secr, insulin release index; SI, sensitivity index; $S_{y \times x}$, residual error of regression; WHR, waist-to-hip ratio.

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

The oral glucose tolerance test (OGTT) is a widely used procedure that was originally developed to classify carbohydrate tolerance (1). However, because plasma glucose and insulin responses during this test reflect the ability of pancreatic β-cells to secrete insulin and the sensitivity of tissues to insulin (2), the OGTT has also been often used to evaluate β-cell function and insulin resistance (3–5). In epidemiological studies, for example, fasting plasma insulin concentrations have been used as an index of insulin resistance, and the 30-min ratio of changes in plasma insulin and glucose have been used as an index of β-cell function (6,7).

Although such approaches are simple, they have not been fully validated. On the other hand, hyperglycemic and euglycemic-hyperinsulinemic clamp studies are well established for assessing β-cell function and insulin sensitivity (8,9), but these are complicated procedures, and they are generally impractical for use outside of specialized research centers. Thus, for epidemiological studies, screenings of high-risk populations, and large-scale intervention trials, simpler methods are desirable.

In the present experiments, we studied 104 healthy nondiabetic volunteers and used multiple linear regression analysis to determine whether plasma glucose and insulin responses during the OGTT in addition to demographic data (e.g., age, sex, BMI) could be used to predict β-cell function and insulin sensitivity as measured by the hyperglycemic and euglycemic-hyperinsulinemic clamp procedures. Because the resultant predictive equations were superior to other methods in common use, we advocate them as a method to assess β-cell function and insulin resistance in situations in which clamp experiments are not feasible.

RESEARCH DESIGN AND METHODS

Subjects

We studied 104 nondiabetic Caucasian volunteers with the following characteristics: 39 men and 65 women, aged means ± SD (range) 45 ± 10 years (21–68), BMI 27.6 ±

Table 1—*Simple linear correlation matrix between MCR, 1st PH, and 2nd PH and demographic parameters and values obtained during the OGTT*

	MCR	ISI	1st PH	2nd PH
Age	−0.29*	−0.29*	−0.08	−0.11
BMI	−0.67†	−0.66†	0.33†	0.35†
WHR	−0.46†	−0.43†	0.13	0.23†
$Gluc_0$	−0.37†	−0.42†	−0.01	0.09
$Gluc_{30}$	−0.27*	−0.28*	−0.18	−0.06
$Gluc_{60}$	−0.37†	−0.38†	−0.25‡	−0.23
$Gluc_{90}$	−0.49†	−0.51†	−0.18	−0.20
$Gluc_{120}$	−0.46†	−0.45†	−0.14	−0.18
AUC Gluc	−0.45†	−0.46†	−0.24	−0.26
Ins_0	−0.56†	−0.59†	0.53†	0.57†
Ins_{30}	−0.34†	−0.34†	0.69†	0.72†
Ins_{60}	−0.46†	−0.49†	0.52†	0.57†
Ins_{90}	−0.60†	−0.62†	0.38†	0.43†
Ins_{120}	−0.62†	−0.62†	0.38†	0.44†
AUC Ins	−0.56†	−0.58†	0.63†	0.62†

Data are correlation coefficients (*r*). *$P < 0.01$; †$P < 0.0005$; ‡$P < 0.05$.

0.5 kg/m^2 (19.7–45.8), and waist-to-hip ratio (WHR) 0.84 ± 0.10 (0.67–1.03); 65 had normal glucose tolerance (NGT), and the remainder had impaired glucose tolerance (IGT) according to the World Health Organization criteria (1). Within 2 months, all subjects underwent a 75-g OGTT, a hyperglycemic clamp study in which the arterialized venous plasma glucose concentration was increased to 10 mmol/l for 180 min, and a euglycemic-hyperinsulinemic clamp study (5 mmol/l) in which insulin was infused at a rate of 1 mU · kg^{-1} · min^{-1} for 180 min. Data for some of the subjects have been reported elsewhere (10,11).

Procedures

OGTT. After a 10-h overnight fast, subjects ingested a solution containing 75 g of dextrose, and venous blood samples were obtained at 0, 30, 60, 90, and 120 min for determination of plasma glucose and plasma insulin (1).

Hyperglycemic and euglycemic-hyperinsulinemic clamp studies. Subjects were admitted to a clinical research unit the evening before the experiments, were given a standard diet between 5:30 and 6:30 P.M., and were studied after an overnight fast. To obtain arterialized blood samples, retrograde cannulation was performed on a hand vein between 7:00 and 8:00 A.M.; the hand was then maintained in a thermoregulated box at 65°C. At the same time, an antecubital vein was cannulated for the infusion of insulin and/or glucose. Reagents were prepared, and the clamp studies were performed as previously described (12).

In the hyperglycemic clamp experiment, samples for plasma insulin determination (Pharmacia Insulin RIA; Kabi Pharmacia Diagnostics, Piscataway, NJ) were taken at −30, −15, 0, 2.5, 5.0, 7.5, 10, 20, 40, 60, 80, 100, 120, 140, 160, and 180 min. In the euglycemic-hyperinsulinemic clamp experiments, samples for plasma insulin were collected at 10- to 20-min intervals. In both clamp experiments, plasma glucose was determined at 5-min intervals using a glucose analyzer (YSI, Yellow Springs, OH), and glucose infusion rates were calculated at 10- to 20-min intervals.

Calculations and statistical analysis

Individual phases of insulin release were evaluated as follows: first-phase insulin release (1st PH) was considered to be the sum of plasma insulin concentrations at 2.5, 5.0, 7.5, and 10 min of the hyperglycemic clamp experiment minus the mean basal plasma insulin concentration, and second-phase insulin release (2nd PH) was considered to be the average plasma insulin concentration during the last hour of the hyperglycemic clamp when plasma insulin concentrations were expected to plateau minus the mean basal plasma insulin concentration (12). Insulin sensitivity was assessed as the metabolic clearance rate (MCR) of glucose calculated as the average glucose infusion rate during the last hour of the euglycemic clamp divided by the average glucose concentration during the same interval (ml · kg^{-1} · min^{-1}). Insulin sensitivity was also assessed as the insulin sensitivity index (ISI) calculated as the average glucose infusion rate divided by the average glucose concentration during the same interval (μmol · kg^{-1} · min^{-1} · pmol/l^{-1}).

Table 2—*Comparison of various indices for insulin sensitivity in the literature (simple linear correlation matrix)*

	MCR_{est} OGTT	ISI_{est} OGTT	IR_{HOMA}	$1/IR_{HOMA}$	ISI Cederholm	ISI(comp) Matsuda	Ins_{120}
MCR (clamp)	0.80	0.79	−0.56	0.58	0.58	0.66	−0.62
ISI (clamp)	0.79	0.79	−0.59	0.59	0.60	0.66	−0.62

Data are correlation coefficients (*r*). $P < 0.0005$ for all values. est, the parameters derived from the model proposed in this article.

Table 3—*Comparison of various indices of insulin release in the literature (simple linear correlation matrix)*

	1st PH_{est} OGTT	2nd PH_{est} OGTT	$Secr_{HOMA}$	ΔIns_{30}	$\Delta Ins_{30}/Gluc_{30}$	$\Delta Ins_{30}/\Delta Gluc_{30}$	AUC_{Ins}/AUC_{Gluc}
1st PH (clamp)	0.78*	0.78*	0.57*	0.63*	0.66*	0.25†	0.71*
2nd PH (clamp)	0.79*	0.79*	0.62*	0.59*	0.60*	0.22‡	0.73*

Data are correlation coefficients (*r*). *$P < 0.0005$; †$P < 0.01$; ‡$P < 0.05$. est, the parameters derived from the model proposed in this article.

Forward stepwise multiple linear regression analysis was performed with the MCR, ISI, 1st PH, and 2nd PH as the dependent variables and demographic parameters and glucose and insulin concentrations during the OGTT as the independent variables (Table 1). Estimates for the MCR, ISI, 1st PH, and 2nd PH were then calculated using the regression equation derived from multiple linear regression. The same calculations were performed using log-transformed values for the MCR, ISI, insulin secretion parameters, and insulin concentrations. Furthermore, the model was also calculated with a parameter for sex as an independent variable. In addition to the correlation coefficient, the SD of the residual error of regression ($S_{y \times x}$) was calculated as a measure of the random error about the regression line (13).

β-cell function and insulin sensitivity were also assessed by using previously proposed parameters such as the homeostasis model assessment (HOMA), the Cederholm index (14), and the composite index [ISI(comp)] proposed by Matsuda (15). The insulin resistance index (IR_{HOMA}) was calculated as follows: $IR_{HOMA} = Ins_0$ (pmol/l) $\times$ $Gluc_0$ (mmol/l)/135, where "Ins" is the plasma insulin concentration during the OGTT, and "Gluc" is the plasma glucose concentration during the OGTT. The insulin release index ($Secr_{HOMA}$) was calculated as follows: $Secr_{HOMA} = Ins_0$ (pmol/l) $\times$ 3.33/[$Gluc_0$ (mmol/l) – 3.5] (16). The sensitivity index (SI) proposed by Cederholm et al. (14) was calculated as SI = [75,000 + ($Gluc_0 - Gluc_{120}$) $\times$ 1.15 $\times$ 180 $\times$ 0.19 $\times$ body weight]/[120 $\times$ log(Ins_{mean}) $\times$ $Gluc_{mean}$]. The ISI(comp) proposed by Matsuda was calculated as

$$10,0000/\sqrt{Gluc_0 \times INS_0 \times Gluc_{mean} \times INS_{mean}}.$$

Ins_t and $Gluc_t$ represent the insulin and glucose concentrations, respectively, at time *t*. Ins_{mean} and $Gluc_{mean}$ represent the mean insulin and glucose concentrations, respectively, during the OGTT. Indices for insulin sensitivity and insulin secretion were compared with the MCR, ISI, 1st PH, and 2nd PH derived from the various models using simple linear regression. The model was also calculated by using log-transformed values for dependent and independent variables. A validation of the model was performed for the MCR, ISI, 1st PH, and 2nd PH, respectively, using the "jackknife" technique, which produces an estimate of the prospective accuracy of a mathematical rule when applied to a completely different sample of subjects (17). For this purpose, one subject was removed from the equations, and the equations were analogously calculated by using the remaining 103 subjects. For the subject removed, a predicted value was determined on the basis of the 103 subjects. This was repeated until predicted values were determined for every subject in the sample. The linear correlation coefficient between the measured and the predicted values was used as an estimate of the goodness of fit. The statistical software package SPSS/PC+ (SPSS, Chicago) was used.

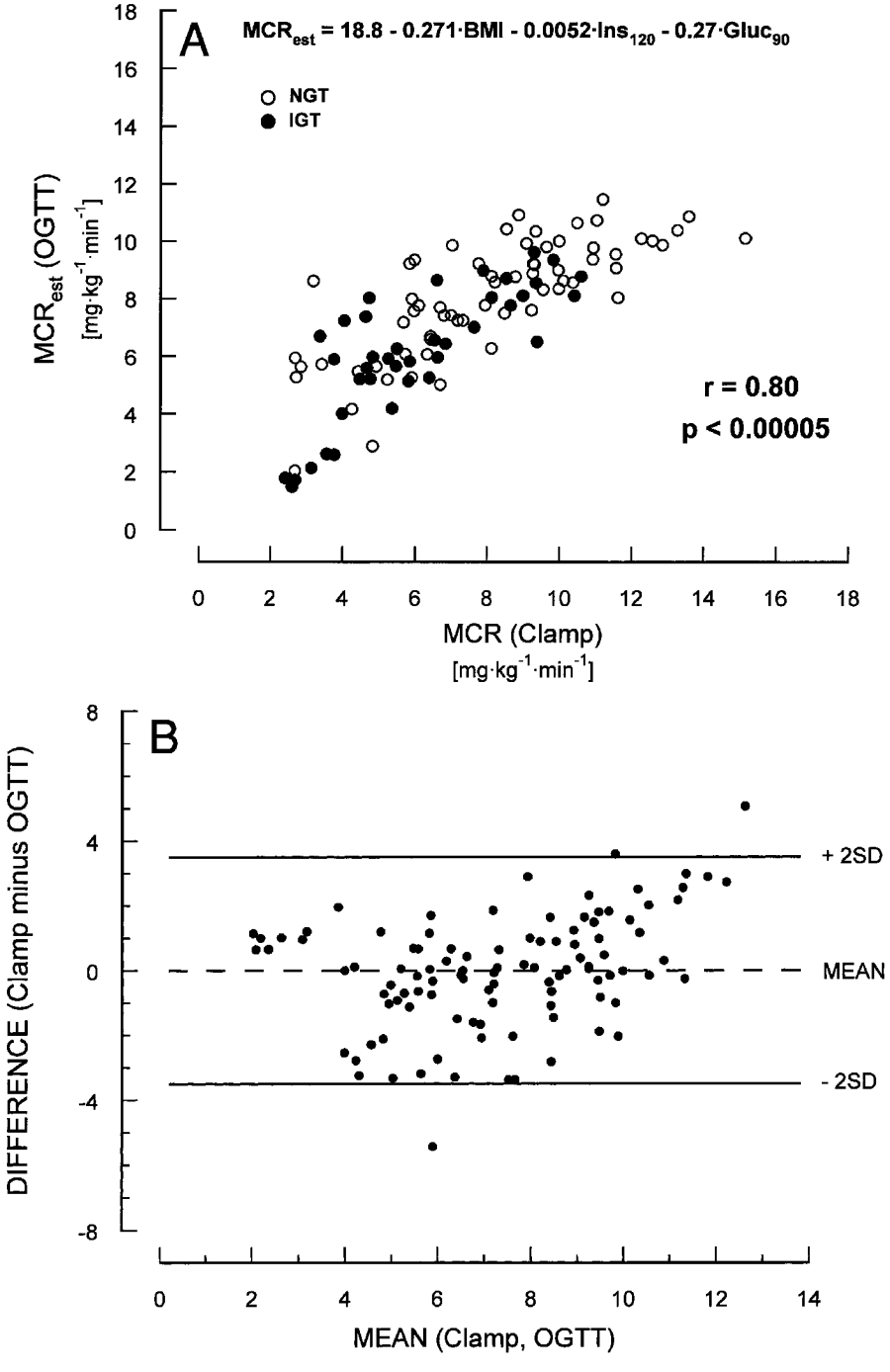

Figure 1—*Linear correlation (A) and Altman-Bland plots (B) between measured MCR (euglycemic clamp) and estimated MCR (OGTT) in 104 nondiabetic subjects (65 with NGT and 39 with IGT). est, the parameters derived from the model proposed in this article.*

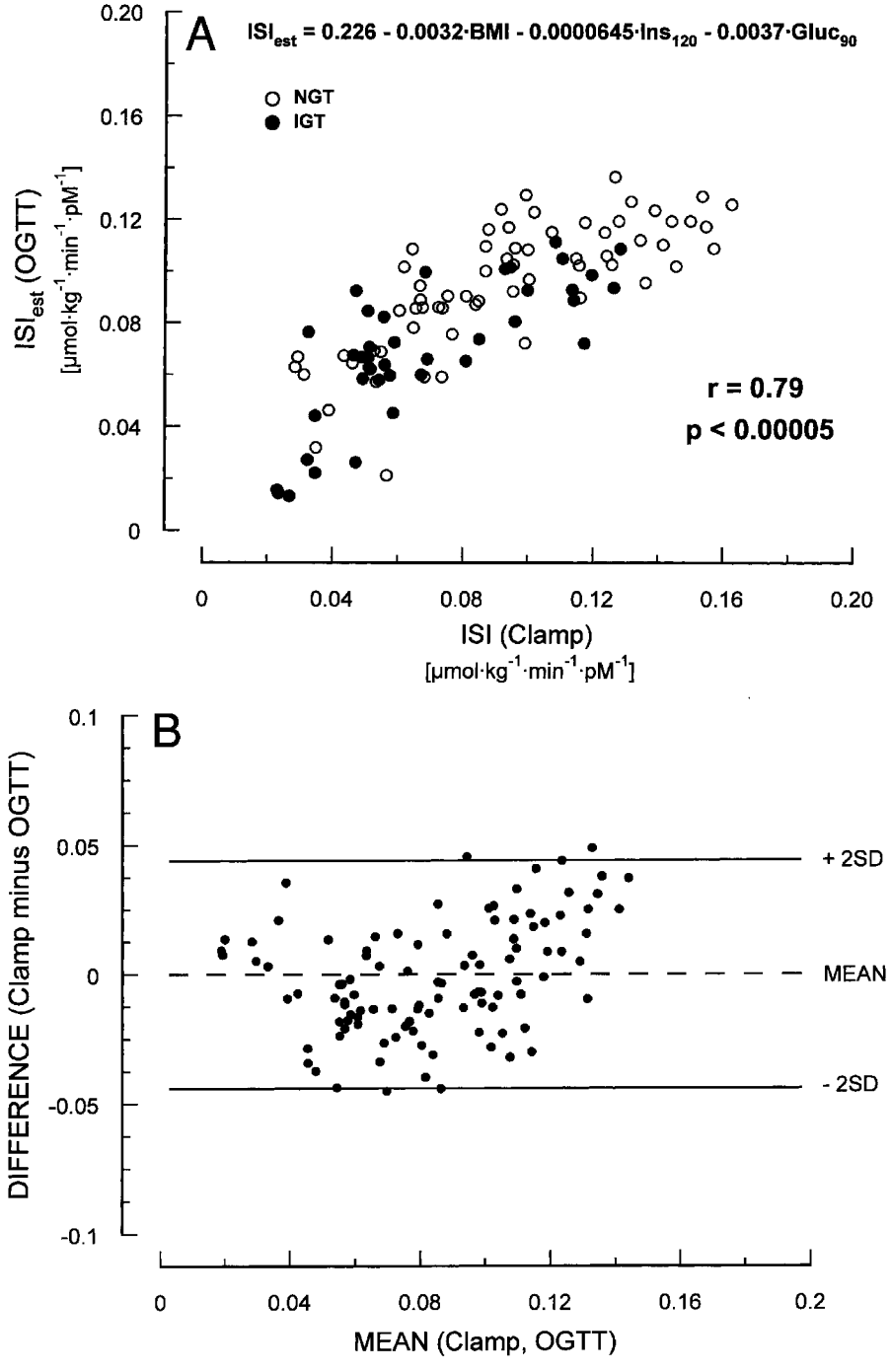

Figure 2—*Linear correlation (*A*) and Altman-Bland plots (*B*) between measured ISI (euglycemic clamp) and estimated ISI (OGTT) in 104 nondiabetic subjects (65 with NGT and 39 with IGT). est, the parameters derived from the model proposed in this article.*

RESULTS

Predictors of insulin sensitivity

As shown in Table 1, with simple linear regression, clamp determinations of insulin sensitivity (MCR, ISI) and β-cell function (1st PH and 2nd PH) were correlated to various degrees with numerous demographic and OGTT parameters. For example, the fasting and 120-min plasma insulin concentrations, which are often used as indices of insulin sensitivity, were correlated to a comparable degree with the MCR, 1st PH, and 2nd PH.

However, as shown in Tables 2 and 3, by using multiple linear regression, only a few of the demographic and OGTT parameters contributed significantly in explaining variations in insulin sensitivity and β-cell function. Inclusion of additional parameters did not increase the variation in insulin sensitivity explained by BMI, the 120-min OGTT plasma insulin concentration, and the 90-min OGTT plasma glucose concentration: MCR = 18.8 – 0.271 × BMI – 0.0052 × Ins_{120} – 0.27 × $Gluc_{90}$ (multiple r = 0.80, $P < 0.00005$, $S_{y \times x}$ = 1.4) (Fig. 1). The same parameters remained in the equation for the ISI: ISI = 0.226 – 0.0032 × BMI – 0.0000645 × Ins_{120} – 0.00375 × $Gluc_{90}$ (multiple r = 0.79, $P < 0.00005$, $S_{y \times x}$ = 0.017) (Fig. 2). These correlations were similarly robust in NGT subjects (MCR: r = 0.77, $P < 0.00005$; ISI: r = 0.77, $P < 0.00005$) and in IGT subjects (MCR: r = 0.79, $P < 0.00005$; ISI: r = 0.77, $P < 0.00005$). Using only glucose and insulin concentrations from the OGTT but not demographic parameters in the multiple linear regression analysis yielded the following equations: MCR = 13 – 0.0042 × Ins_{120} – 0.384 × $Gluc_{90}$ – 0.0209 × Ins_0 (r = 0.686, $P < 0.00005$) and ISI = 0.157 – 4.576 × 10^{-5} × Ins_{120} – 0.00519 × $Gluc_{90}$ – 0.000299 × Ins_0 (r = 0.707, $P < 0.00005$).

Predictors of β-cell function

Similarly, β-cell function as reflected by 1st PH and 2nd PH during the hyperglycemic clamp studies could largely be predicted by the 0- and 30-min plasma insulin value during the OGTT and the 30-min plasma glucose value during the OGTT (Figures 3 and 4). Inclusion of additional parameters did not increase the variation in 1st PH and 2nd PH explained by these three variables: 1st PH = 1,283 + 1.829 × Ins_{30} – 138.7 × $Gluc_{30}$ + 3.772 × Ins_0 (multiple r = 0.78, $P < 0.00005$, $S_{y \times x}$ = 277) and 2nd PH = 287 + 0.4164 × Ins_{30} – 26.07 × $Gluc_{30}$ + 0.9226 × Ins_0 (multiple r = 0.79, $P < 0.00005$, $S_{y \times x}$ = 61). Inclusion of a sex parameter did not affect the model.

Using log-transformed values did not substantially alter the correlation coefficients (MCR: multiple r = 0.78, $P < 0.00005$; ISI: multiple r = 0.78, $P < 0.00005$; 1st PH: multiple r = 0.72, $P < 0.00005$; 2nd PH: multiple r = 0.71, $P < 0.00005$). These correlations were similarly robust in NGT subjects (1st PH: r = 0.70, $P < 0.00005$; 2nd PH: r = 0.76, $P < 0.00005$) and in IGT subjects (1st PH: r = 0.87, $P < 0.00005$; 2nd PH: r = 0.80, $P < 0.00005$).

Comparisons with other approaches

The "jackknife" validation procedure of the derived equations yielded reasonably high correlations between the estimated and the measured values for MCR and ISI (both $r = 0.77$, $P < 0.0005$), 1st PH ($r = 0.74$, $P < 0.0005$), and 2nd PH ($r = 0.76$, $P < 0.0005$). As shown in Table 2, insulin sensitivity (measured MCR and ISI) was best correlated with MCR and ISI predicted from the OGTT-derived equations, followed by ISI(comp), Ins_{120}, IR_{HOMA}, and the sensitivity index proposed by Cederholm (14). Similarly, β-cell function (measured 1st PH and 2nd PH) was best correlated with values predicted by equations from the OGTT, followed by area under the curve (AUC) Ins/AUC Gluc, $\Delta Ins_{30}/Gluc_{30}$, $Secr_{HOMA}$, and $\Delta Ins_{30}/\Delta Gluc_{30}$.

CONCLUSIONS — The present studies demonstrate that predicting an individual's insulin sensitivity and β-cell function from BMI and values for plasma glucose and insulin obtained during an OGTT is possible. Using these parameters in an equation derived from multiple linear regression predicted insulin sensitivity as reflected by MCR and ISI and β-cell function as reflected by 1st PH and 2nd PH with reasonable accuracy (r values of >0.75) and better than several commonly used simple methods. In addition, the Altman-Bland plots demonstrate that only very few points (~5%) are outside 2 SD, which indicates a reasonable specificity over the entire range. The mean differences (measured minus predicted parameter) of ~0 indicate that the parameters derived from the OGTT do not contain a systematic bias.

The $\Delta Ins_{30}/\Delta Gluc_{30}$ ratio, which is widely used as an index of β-cell function (18–20), was found to correlate rather poorly with actually measured β-cell function. Moreover, fasting and 120-min plasma insulin concentrations, which are commonly used as indicators of insulin resistance, were found to be correlated also with β-cell function when using simple linear regression, which indicates the poor rationale for this practice.

Age was not found to be an independent determinant of either insulin sensitivity or β-cell function. Although data from some cross-sectional studies suggest that insulin sensitivity (21–23) and β-cell function (24–26) decrease as a function of age, other studies have shown no effect (25,27,28). Regarding insulin sensitivity, inclusion of BMI and WHR, which both increase with age (28), may be responsible because the effects of aging are mediated through changes in body composition.

Regarding β-cell function in which neither BMI, WHR, nor age were found to be independent predictors, this observation is more difficult to explain, especially because obese individuals are often hyperinsulinemic (29). A possible explanation is that inclusion of the 30-min OGTT glucose value along with the insulin response at that time in the equations for insulin release take into consideration an individual's insulin sensitivity, which is a function of BMI and/or WHR.

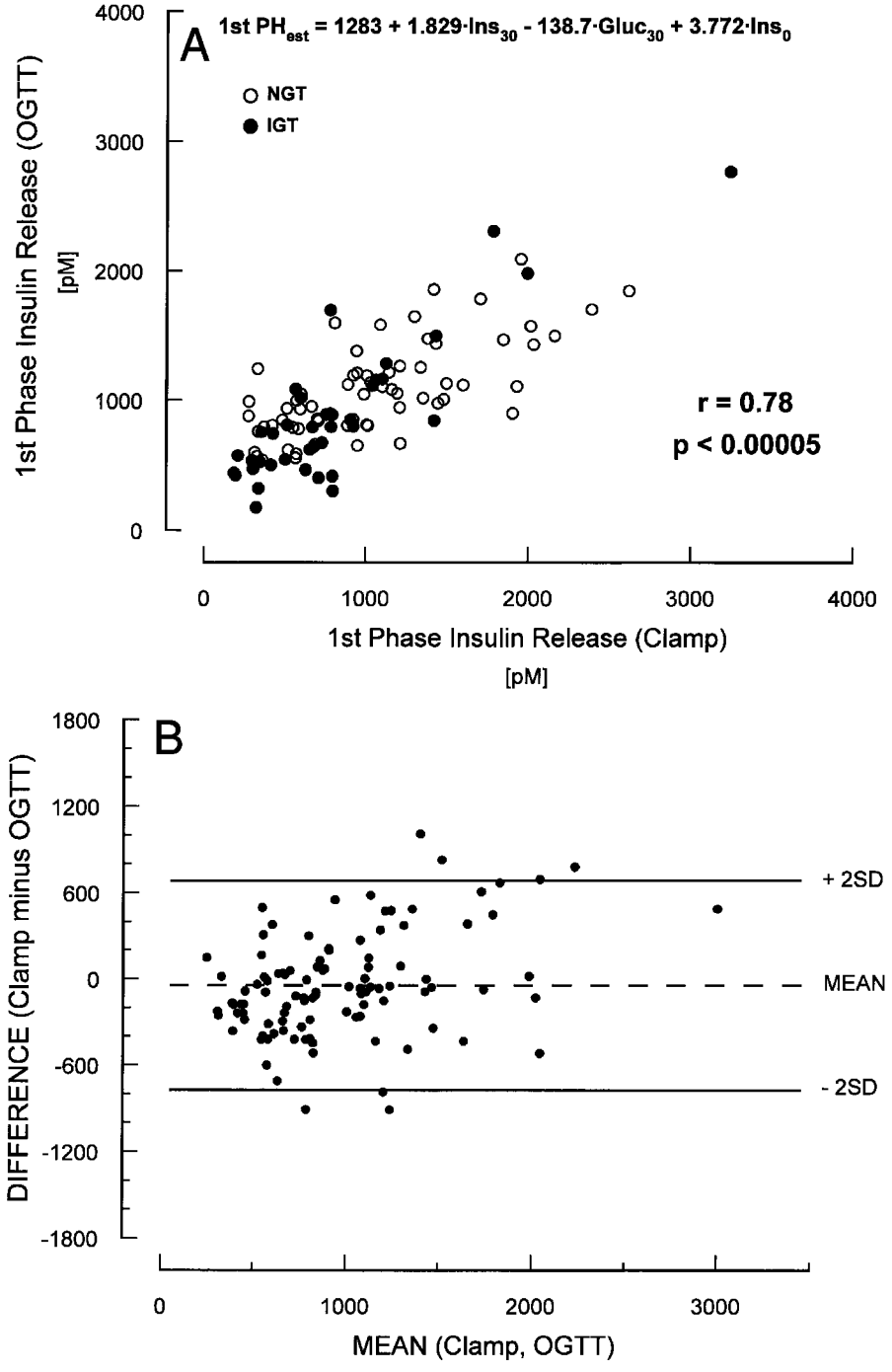

Figure 3—*Linear correlation (*A*) and Altman-Bland plots (*B*) between measured 1st PH (hyperglycemic clamp) and estimated 1st PH (OGTT) in 104 nondiabetic subjects (65 with NGT and 39 with IGT). est, the parameters derived from the model proposed in this article.*

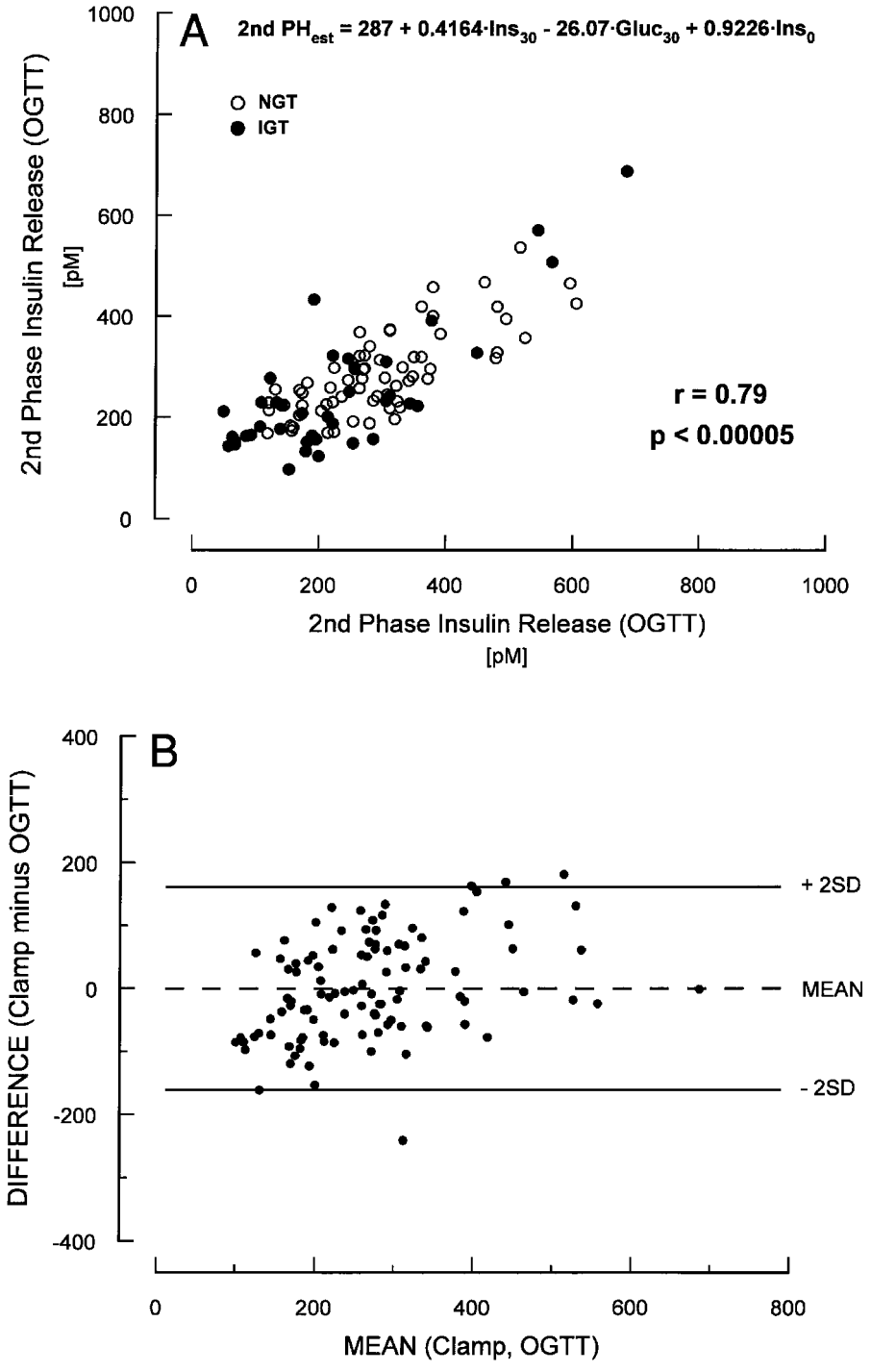

Figure 4—*Linear correlation (*A*) and Altman-Bland plots (*B*) between measured 2nd PH (hyperglycemic clamp) and estimated 2nd PH (OGTT) in 104 nondiabetic subjects (65 with NGT and 39 with IGT). est, the parameters derived from the model proposed in this article.*

The equations derived in the present study were obtained in an adult nondiabetic europid white population that ranged in age from 21 to 68 years and in obesity (BMI) from 19.7 to 45.8 kg/m^2. To what extent these or similar equations would be applicable in different populations (e.g., in noneuropids, children, or extremely lean or diabetic individuals) remains to be determined.

Nevertheless, because of the ease of obtaining data for the equations derived in the present study, the equations may be of value in evaluating insulin sensitivity and β-cell function in various circumstances in which the use of clamps or the minimal model is impractical.

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