Homeostasis Model Assessment Closely Mirrors the Glucose Clamp Technique in the Assessment of Insulin Sensitivity

Studies in subjects with various degrees of glucose tolerance and insulin sensitivity

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OBJECTIVE — To evaluate whether the homeostasis model assessment (HOMA) is a reliable surrogate measure of in vivo insulin sensitivity in humans.

RESEARCH DESIGN AND METHODS — In the present study, we compared insulin sensitivity as assessed by a 4-h euglycemic ($\sim$5 mmol/l) hyperinsulinemic ($\sim$300 pmol/l) clamp with HOMA in 115 subjects with various degrees of glucose tolerance and insulin sensitivity.

RESULTS — We found a strong correlation between clamp-measured total glucose disposal and HOMA-estimated insulin sensitivity (r = −0.820, P < 0.0001), with no substantial differences between men (r = −0.800) and women (r = −0.796), younger (aged <50 years, r = −0.832) and older (r = −0.800) subjects, nonobese (BMI <27 kg/m^2, r = −0.800) and obese (r = −0.765) subjects, nondiabetic (r = −0.754) and diabetic (r = −0.695) subjects, and normotensive (r = −0.786) and hypertensive (r = −0.762) subjects. Also, we found good agreement between the two methods in the categorization of subjects according to insulin sensitivity (weighted k = 0.63).

CONCLUSIONS — We conclude that the HOMA can be reliably used in large-scale or epidemiological studies in which only a fasting blood sample is available to assess insulin sensitivity.

Diabetes Care 23:57–63, 2000

S everal studies consistently demonstrated that insulin resistance is a strong predictor of type 2 diabetes (1,2). More recently, insulin resistance has been shown to be associated with prevalent atherosclerosis (3–5). Thus, the recognition of insulin resistance seems to have investigational and clinical relevance in identifying subjects at high risk of type 2 diabetes and/or cardiovascular disease.

Insulin resistance can be measured by using the glucose clamp technique (6), which is regarded as the reference method for an accurate assessment of in vivo insulin sensitivity (7). However, this method is laborious, expensive, and therefore unsuitable for large-scale or epidemiological studies. Several alternative methods to evaluate insulin sensitivity have been proposed during the last two decades (8–13), but, although generally less complex and less troublesome than the glucose clamp technique, none of them is as simple as is necessary in large-scale studies involving hundreds or thousands of subjects.

Homeostasis model assessment (HOMA) of insulin sensitivity was proposed about 10 years ago as a simple and inexpensive alternative to more sophisticated techniques (14). Such a method derives an estimate of insulin sensitivity from the mathematical modeling of fasting plasma glucose and insulin concentrations. Although the HOMA has been recently used in several clinical and epidemiological studies (15–24), it has not been definitely validated. Indeed, few data are available that compare insulin sensitivity estimated by the HOMA with that measured by the glucose clamp technique (12,25,26).

In the present study, we performed euglycemic hyperinsulinemic clamp studies in combination with tracer glucose infusion to measure insulin-stimulated glucose disposal in 115 individuals with various degrees of glucose tolerance and insulin sensitivity and compared the clamp studies with the estimate of insulin sensitivity derived by the HOMA.

RESEARCH DESIGN AND METHODS

Subjects

The study included 115 subjects who all underwent a glucose clamp with the format described below in our laboratory in 1995 and 1996. A total of 53 subjects with type 2 diabetes was recruited among those

Table 1—*Main clinical characteristics of subjects under study*

	Subjects	
	Nondiabetic	Type 2 diabetic
Sex (M/F)	12/50	37/16
Age (years)	41.3 ± 1.4 (19 to 63)	55.6 ± 1.0 (31 to 67)
Body weight (kg)	76.9 ± 2.2 (53 to 115)	75.9 ± 1.4 (52 to 104)
BMI (kg/m^2)	27.8 ± 0.7 (19 to 45)	27.7 ± 0.6 (20 to 51)
Waist-to-hip ratio	0.88 ± 0.01 (0.73 to 1.04)	0.97 ± 0.01 (0.83 to 1.01)
Fasting insulin (pmol/l)	63 ± 4 (21 to 182)	96 ± 7 (14 to 224)
Fasting glucose (mmol/l)	5.0 ± 0.05 (4.3 to 6.0)	9.72 ± 0.35 (4.4 to 16.2)
HbA$_{1c}$ (%)	—	6.6 ± 0.2 (4.2 to 9.0)
HOMA score	2.06 ± 0.14 (0.7 to 6.5)	5.98 ± 0.48 (1.1 to 13.9)
TGD during clamp (µmol · min^{-1} · kg^{-1} fat-free mass)	34.6 ± 1.6 (17.4 to 75.9)	21.0 ± 1.1 (7.8 to 52.5)
Glucose rate of appearance during clamp (µmol · min^{-1} · kg^{-1} fat-free mass)	0.92 ± 0.50 (−6.39 to 8.28)	4.1 ± 0.7 (−5.4 to 13.4)
Hypertension (%) (≥160/95 mmHg or treatment)	25.8	56.6
Obesity (%)	41.9	37.7

Data are means ± SEM (range) or %.

regularly attending the Diabetes Clinic at the University of Verona who were willing to participate in the study. Of these patients, 10 were treated with diet only, and 43 were taking oral hypoglycemic agents (22 were taking sulfonylureas, 21 were taking sulfonylureas plus metformin). Patients taking insulin were excluded from the study, and 62 nondiabetic subjects were recruited by an advertisement. All participants underwent a physical examination and routine blood chemistry evaluation. None of them had a history of recent acute illness or clinical evidence of cardiovascular, kidney, liver, or endocrine diseases. Body composition was measured by using bioimpedance analysis (27). Main clinical features of the study subjects are shown in Table 1. All subjects gave their written informed consent to participate in the study. The protocol was approved by the Ethical Committee of the Verona City Hospital.

Glucose clamp

The study consisted of a 4-h euglycemic hyperinsulinemic clamp. The clamp was carried out as originally described by De-Fronzo et al. (6), with the exception of the amount of insulin infused, which was lower in the present study than that used in the pioneering article by DeFronzo et al. The insulin amount was lowered to achieve serum insulin levels resembling those encountered after a meal. The clamp was performed in combination with 3-[^{3}H]-D-glucose infusion, as previously reported in detail (28), to assess total glucose disposal (TGD) accurately.

All studies began at 8:00 A.M. Subjects were admitted to the hospital after a 10- to 12-h overnight fast. Briefly, two Teflon cannulas were inserted: one was inserted into an antecubital vein for infusion of insulin, glucose (20% dextrose), and 3-[^{3}H]-D-glucose, and the other was inserted into a contralateral heated (~60°C) hand vein for arterialized blood sampling. After baseline blood collections for glucose and insulin determinations, a prime constant (20 mU · min^{-1} · m^{-2} body surface area) insulin infusion was started and continued for the subsequent 240 min. The insulin prime consisted of two subsequent 5-min periods during which insulin was infused at the rate of 80 and 40 mU · min^{-1} · m^{-2}, respectively.

In nondiabetic subjects, serum insulin increased from an average basal value of 76 ± 10 to a mean concentration of 292 ± 38 pmol/l in the last hour of the clamp, whereas the values were 108 ± 14 and 304 ± 42 pmol/l, respectively, in the diabetic subjects. Plasma glucose was clamped at ~5 mmol/l by a variable glucose infusion. In diabetic subjects, plasma glucose was left to drop until euglycemia was reached (generally within 120 min) and then was maintained at that level. In the last hour of the clamp, plasma glucose variability (co-efficient of variation [CV]) was <5% in all subjects. At 2 h after the beginning of the glucose clamp, a prime constant infusion of 3-[^{3}H]-D-glucose was initiated at the rate of 0.45 µCi/min and was continued until the end of the study. The prime dose of labeled glucose was calculated by dividing the glucose pool (plasma glucose concentration × glucose distribution volume assumed to be 25% of body weight) by the product of 1.1 by the glucose infusion rate (GIR) from 100 to 120 min of the study and then multiplying the result by the tracer infusion rate. GIR was multiplied by 1.1 to take into account the expected 10% average increase in GIR from 100–120 to 180–240 min of the glucose clamp. As previously reported (29), with this methodological approach, a steady state of tritiated glucose specific activity is obtained from 180 to 240 min of the clamp. In fact, in the entire group we examined, mean specific activity at 180 min and at 240 min averaged 843 ± 32 and 821 ± 33 dpm/µmol, respectively, with a CV of 2.5 ± 0.3% from 180 to 240 min. During this period, blood was drawn every 10 min to measure plasma levels of glucose, serum insulin, and plasma tritiated glucose specific activity. Insulin-mediated TGD rate was calculated by dividing the 3-[^{3}H]-D-glucose infusion rate by the steady-state 3-[^{3}H]-D-glucose specific activity. More details have been reported elsewhere (28).

Analytical determinations

Plasma glucose was measured by using the glucose oxidase method on a Beckman Glucose Analyzer (Fullerton, CA). Serum insulin was measured by using a double-antibody radioimmunoassay without cross-reactivity with proinsulin or split-proinsulin products (Linco Research, St. Louis, MO). The intra- and interassay CVs of serum insulin were 2.9 and 4.7%, respectively. Plasma 3-[^{3}H]-D-glucose specific activity was determined as previously described in detail elsewhere (28).

HOMA of insulin resistance

The estimate of insulin resistance by HOMA score was calculated with the formula: fasting serum insulin (µU/ml) × fasting plasma glucose (mmol/l)/22.5, as described by Matthews and coworkers (12). With such a method, high HOMA scores denote low insulin sensitivity (insulin resistance). The CVs of HOMA scores were 9.4 ± 0.7 and 7.8 ± 0.6%, re-
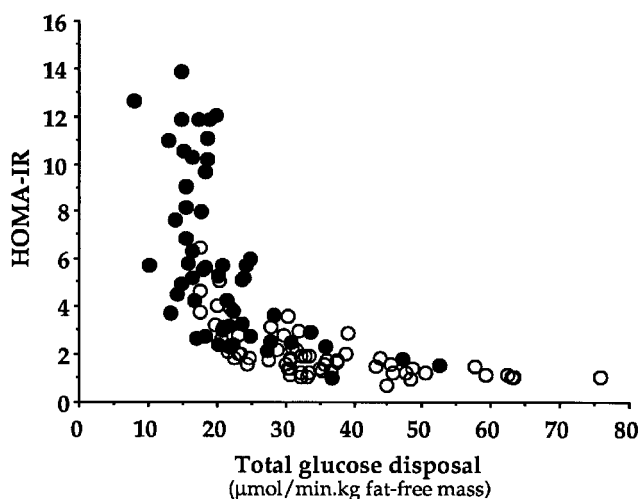
Figure 1—Scatterplot of TGD rates ($\mu mol \cdot min^{-1} \cdot kg^{-1}$ fat-free mass) in the 4th h of a euglycemic (~5 mmol/l) hyperinsulinemic (~300 pmol/l) clamp and HOMA scores in 115 subjects. ○, Nondiabetic subjects; ●, type 2 diabetic subjects. Linear regression: r = −0.627, P <0.0001; polynomial regression: r = −0.743, P < 0.0001. IR, insulin resistance.

metric correlation (R_s = −0.855, P < 0.0001). The degree of linear correlation between log HOMA scores and log TGD rates was very similar between men and women (−0.800 vs. −0.796), younger (<50 years) and older (−0.832 vs. −0.800) subjects, nonobese (BMI <27 kg/m²) and obese (−0.800 vs. −0.765) subjects, nondiabetic and diabetic (−0.745 vs. −0.695) subjects, and normotensive and hypertensive (−0.786 vs. −0.762) subjects. Thus, the results were consistent within all categories of interest.

The agreement in the categorization was good according to insulin sensitivity when subjects were stratified into quintiles of HOMA scores and TGD rates (weighted k = 0.63) (Table 2). In particular, when considering that the categories of higher insulin sensitivity corresponded to quintile V of TGD and to quintile I of HOMA and that the categories of greater insulin resistance corresponded to quintile I of TGD and to quintile V of HOMA, we found same-category agreement in 46% of subjects, one-quintile disagreement in 49% of subjects, and two-quintile disagreement in only 5% of subjects. Three- or four-quintile disagreement never occurred.

CONCLUSIONS — Insulin resistance plays a major role in the development of type 2 diabetes (1,2,30) and may also be involved in atherogenesis (3–5). Thus, the assessment of insulin sensitivity has become a frequent need for clinical investi-

spectively, in 20 nondiabetic subjects and 20 diabetic individuals in whom this parameter was measured three times in the fasting state at 5-min intervals. The CVs of HOMA scores were 13.8 and 11.2%, respectively, in a single nondiabetic subject and in a single diabetic subject in whom this parameter was measured in the morning for 5 consecutive days.

Statistical analysis
HOMA scores and TGD rates during the glucose clamp were log-transformed to approximate a normal distribution. Linear and polynomial regressions, Pearson's simple correlations, and Spearman's rank correlations between HOMA scores and TGD rates were computed. HOMA scores and TGD rates in each individual were stratified into quintiles, and Cohen's k coefficient of agreement (weighted k) was computed. Weights for agreement were set at 0.00 (full disagreement), 0.25, 0.50. 0.75, and 1.00 (full agreement). All data are means ± SEM.

RESULTS — The entire group exhibited a strong inverse correlation between TGD rates during the glucose clamp and HOMA scores. With raw data, linear regression analysis gave a Pearson's correlation coefficient of −0.627 (P < 0.0001), but the scatterplot was skewed hyperbolically (Fig. 1). A curvilinear fitting (polynomial regression) of the data gave a correlation coefficient of −0.743 (P < 0.0001).

With log-transformed data, the correlation coefficient between HOMA scores and TGD rates was −0.820 (P < 0.0001) (Fig. 2). The correlation between log HOMA scores and log GIR during the clamp was virtually identical (r = −0.801, P < 0.0001). Thus, from a statistical viewpoint, ~65% of the variability of insulin sensitivity assessed by the glucose clamp technique could be accounted for by HOMA. The nonparametric Spearman's rank correlation was similar to the para-
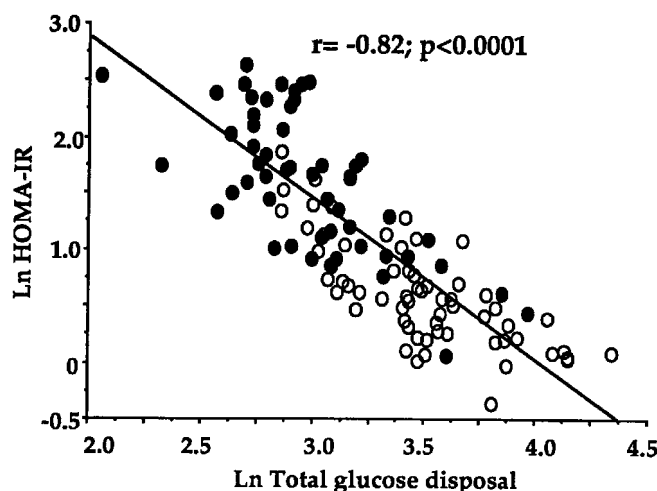

Figure 2—Simple correlation between log-transformed TGD rates ($\mu mol \cdot min^{-1} \cdot kg^{-1}$ fat-free mass) in the 4th hour of a euglycemic (~5 mmol/l) hyperinsulinemic (~300 pmol/l) clamp and log-transformed HOMA scores in 115 subjects. ○, Nondiabetic subjects; ●, type 2 diabetic subjects. IR, insulin resistance.

Table 2—*Agreement in the categorization of subjects according to insulin sensitivity, as measured by the glucose clamp and as estimated by the HOMA*

TGD quintiles	HOMA quintiles				
	I	II	III	IV	V
I	0	0	1	7	15
II	0	1	7	9	6
III	0	7	8	6	2
IV	9	7	6	1	0
V	14	8	1	0	0

Subjects were stratified into quintiles of TGD rates and HOMA scores. Number of observations in each quintile is reported. Weighted k coefficient of agreement = 0.63. Agreement was based on the assumption that maximum insulin sensitivity corresponded to quintile I of HOMA and quintile V of TGD, and minimum insulin sensitivity corresponded to quintile V of HOMA and quintile I of TGD.

gators and epidemiologists and may also be useful for clinicians.

In recent years, a new clinical syndrome has been described that features the clustering of several metabolic, hemodynamic, and hemocoagulative disorders (31,32). Although this syndrome has been given many names, its most popular name is "insulin resistance syndrome." This name is justified by the idea that insulin resistance is the major common denominator of the abnormalities involved in the syndrome. Unfortunately, the vast majority of data contributing to our knowledge about this syndrome is not based on the true measurement of insulin resistance.

During the last 20 years, the assessment of in vivo insulin sensitivity in humans has been frequently based on the use of the glucose clamp technique (6). This technique is considered the "gold standard" (7), although it does not mirror the physiological condition of continuously changing glucose and insulin levels (with mutual control of the hormone on the substrate and vice versa) and of differing insulin exposure in the liver and peripheral tissues. In this regard, one may conclude that no method will ever be capable of truly measuring insulin sensitivity, but the glucose clamp technique is the method with the fewest drawbacks, and it yields results closest to the real measure. Unfortunately, this technique is not suited for large-scale or epidemiological studies because of its complexity and high cost. Alternative methods have been proposed and used in clinical investigations, but none of them is adequate for studies involving hundreds or thousands of subjects. Indeed, all of these alternative methods include injections and/or infusions of hormones, drugs, or substrates as well as drawing several timed blood samples (8–13).

An attractive approach to estimate insulin sensitivity (or insulin resistance) seems to be the HOMA, which was developed by Matthews et al. (14) with computer-aided modeling of fasting glucose and insulin concentrations. These authors found that the HOMA-based insulin resistance score was strongly correlated with insulin sensitivity assessed by the glucose clamp technique in both nondiabetic and diabetic subjects ($r = -0.83$ and -0.92, respectively) (14). However, validation of the HOMA was carried out in only a few subjects (12 nondiabetic and 11 diabetic), and the glucose clamp studies were not performed in conjunction with glucose tracer infusion, so glucose disposal could not be assessed accurately. Indeed, endogenous glucose production is not always completely suppressed by physiological hyperinsulinemia, especially in diabetic subjects (28–30), and the GIR, which maintains euglycemia during the glucose clamp, can underestimate the exact rate of glucose disposal. In another validation study, Anderson et al. (25) compared the HOMA with the glucose clamp technique in a relatively greater number of subjects (n = 55), half of whom had type 2 diabetes, and found a weaker correlation between the two measures ($r = -0.40$). However, these authors performed isoglycemic and not euglycemic clamp studies, which thereby led to an overestimation of insulin sensitivity in hyperglycemic individuals because of the mass effect of glucose (33). In the only other validation study we are aware of, Emoto et al. (26) compared HOMA and the glucose clamp technique in 80 type 2 diabetic subjects and found a good relationship between the two measures of insulin sensitivity ($r = -0.725$, $P < 0.001$). Unfortunately, no isotopic evaluation of TGD was pursued in this study.

In our study, the glucose clamp methodology was combined with the glucose tracer dilution technique, and the study was performed at euglycemia in both nondiabetic and diabetic subjects. Thus, the experimental conditions were the same in all subjects, which thereby allowed us to gather a comparable measurement of TGD during insulin infusion. In this context, HOMA scores and TGD rates were strongly correlated, and the results were consistent in the various subgroups that we examined (men vs. women, older vs. younger subjects, obese vs. nonobese subjects, diabetic vs. nondiabetic subjects, and hypertensive vs. normotensive subjects). Taken together, these results support the use of the HOMA as a surrogate index of insulin sensitivity in humans. Of course, this conclusion relies on the assumption that TGD during the clamp is the reference measure of insulin sensitivity.

The HOMA score does not measure the amount of glucose metabolized per unit of body weight or lean body mass during whole-body insulinization; rather, the HOMA score explores the spontaneous homeostatic characteristics of a metabolic system by inferring what degree of insulin sensitivity is compatible with these homeostatic characteristics. Nevertheless, the HOMA ranks individuals similarly to the glucose clamp technique. In fact, in a large number of individuals with various degrees of glucose tolerance and insulin resistance, we found a strong correlation between the insulin sensitivity values generated by the two tests. In this regard, the HOMA score seems to be as good a predictor of clamp-determined insulin sensitivity as the short insulin tolerance test (11) or the intravenous glucose tolerance test (IVGTT) analyzed with the minimal model (34–37), the method often indicated as the best alternative to the glucose clamp technique (3,38,39). HOMA precision (reproducibility of the measure) seems to be comparable to the glucose clamp technique and displays a CV (10–15%) that is similar to that observed with the glucose clamp (40; R.C.B., unpublished observations). Unquestionably, the HOMA is inferior to the glucose clamp technique in terms of its accuracy in assessing insulin sensitivity, but the trade-off for this limitation lies in the ease with which large numbers of subjects can be examined with a single glucose and insulin measurement in the fasting state.

One could argue that we have conducted clamp studies at relatively low insulin concentrations. Thus, the question arises whether the agreement of HOMA-estimated and clamp-measured insulin sensitivity persists when the clamp experiment is performed at higher insulin concentrations. During the years, we have collected a large number of clamp studies carried out at 40 or 100 mU · min⁻¹ · m⁻² surface area. We have recently computed the HOMA scores in subjects undergoing these studies and have found strong relationships with TGD rates during the clamp. For example, in a group 19 subjects with various degrees of insulin sensitivity and glucose tolerance undergoing a 40-mU · min⁻¹ · m⁻² surface area clamp (11), we found a correlation coefficient of −0.881. In another series of 47 studies in which the clamp was carried out at supraphysiological insulin concentrations (100 mU · min⁻¹ · m⁻² surface area) (41–43), the coefficient of correlation between HOMA scores and TGD rates was −0.762.

One could also argue that the HOMA score is calculated in the fasting condition, whereas the TGD rate in diabetic subjects was calculated at euglycemia and not at fasting ambient hyperglycemia. Thus, one may wonder whether the two measurements are comparable. We addressed this issue by comparing HOMA scores in five subjects with type 2 diabetes whom we had examined both in the spontaneous fasting state (10.2 ± 1.1 mmol/l) and a few days later after an overnight infusion of low-dose insulin to achieve euglycemia the next morning (4.8 ± 0.4 mmol/l) (44). The mean HOMA scores were quite similar (6.98 ± 1.88 at hyperglycemia and 5.89 ± 2.17 at euglycemia, NS), and the measures on the two separate occasions were strongly correlated (r = 0.889).

Further support for more widespread use of the HOMA comes from several recent studies. For example, Haffner et al. (18) found that insulin resistance estimated by the HOMA predicts the development of type 2 diabetes in Mexicans, which is similar to the observations made in Pima Indians (2) and in Caucasians (1) with the glucose clamp technique and the IVGTT analyzed with minimal model, respectively. Furthermore, Clement et al. (17) found that glucokinase-deficient subjects are insulin resistant either when scored by the HOMA or when evaluated by the glucose clamp technique, yet Zhang et al. (24) found a mutation of the insulin receptor

substrate-1 in type 2 diabetic subjects that resulted in high HOMA scores. Finally, Kumar et al. (20) reported an improvement in HOMA-estimated insulin resistance after troglitazone treatment of type 2 diabetic subjects in agreement with troglitazone effects observed in glucose clamp studies (45). Thus, the HOMA can unravel insulin resistance, whether it is associated with type 2 diabetes or pre–type 2 diabetes, or with a disruption of insulin signaling at the molecular level.

Although definite proof is lacking, it seems reasonable that HOMA cannot be used in patients with type 1 diabetes or in patients with type 2 diabetes receiving insulin treatment because assessing the spontaneous homeostatic characteristics of the metabolic system in these individuals is not possible. However, the data above reporting on the consistency of HOMA scores in type 2 diabetic subjects examined at spontaneous fasting hyperglycemia and at insulin-induced euglycemia could challenge this belief. Further studies are needed to clarify this aspect. Regardless, insulin-treated diabetic subjects represent only a limited fraction of the diabetic population (46). Specific studies are needed regarding the capability of HOMA to assess insulin sensitivity in particular type 2 diabetes phenotypes such as subjects with poor insulin secretion and normal insulin sensitivity or with severe insulin resistance and exhausted β-cells.

In the three previous validation studies (12,25,26), serum insulin was measured by using a standard (not human insulin-specific) radioimmunoassay. In our study, we used an insulin-specific radioimmunoassay with no significant cross-reactivity with proinsulin or split-proinsulin products, thereby minimizing the interference exerted on the HOMA score by raised plasma proinsulin levels, such as those possibly encountered in diabetic subjects (47,48).

HOMA is based on measuring plasma glucose and serum/plasma insulin. Although the plasma glucose assay is known to be highly reproducible in different laboratories, insulin assay can vary considerably, especially if antibodies cross-reacting with proinsulin or split-proinsulin products are used (49). The use of specific anti-insulin antibodies is becoming common, and fewer discrepancies among laboratories are expected to occur in the future. At present, however, comparing HOMA scores generated in different laboratories that used different insulin assay materials

should be done with great caution. For the same reason, the use of HOMA in the clinical setting to identify insulin-resistant subjects is not recommended because a cutoff value for insulin resistance estimated with the HOMA would not be easily defined. Of course, standardization of the insulin assay may circumvent these problems. Unfortunately, standardization of the insulin assay is far from becoming a reality.

One could ask whether a physiological basis underlies the strong relationship we observed between HOMA scores and clamp TGD rates. Indeed, the HOMA is a parameter that essentially explores the ability of insulin to restrain hepatic glucose production in the fasting state because basal insulin has a substantial effect on hepatic glucose production (50) but a quantitatively poor (if any) effect on peripheral glucose disposal (51). On the contrary, clamp TGD is a function mainly of peripheral responses to higher insulin concentrations (28–30). We hypothesize that HOMA scores and clamp TGD rates are strongly correlated because, in virtually all clinical conditions that are characterized by peripheral insulin resistance, hepatic insulin resistance is also evident (28,30,32). This is probably because of the fact that peripheral insulin resistance of glucose metabolism is generally associated with an impaired insulin-suppressed lipolysis (41,43). Indeed, the insulin-signaling mechanisms that control glucose metabolism in the skeletal muscle and lipid metabolism in adipose tissue are somewhat common (52,53) and are thought to be disrupted in insulin-resistant conditions (53). One consequence of the deranged insulin signaling in adipose tissue is an exaggerated lipolysis that leads to an increased flux of free fatty acids from adipocytes to the liver, where they contribute to the diminished ability of insulin to suppress hepatic glucose production (54). Thus, that a parameter addressing essentially hepatic insulin resistance (HOMA score) is strongly related to a parameter describing to a greater extent peripheral insulin resistance (clamp TGD rate) is not surprising.

In conclusion, our data suggest that the HOMA is a valuable alternative to more sophisticated techniques in the evaluation of in vivo insulin sensitivity in humans. The HOMA seems to be specifically suited to large-scale studies in which only fasting blood samples are available. Nevertheless, comparing HOMA scores obtained in different studies cannot be done unless the in-

sulin assay is standardized. Standardization of the insulin assay is also a prerequisite for introducing the HOMA in clinical practice.

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