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Homeostasis Model Assessment and Related Simplified Evaluations of Insulin Sensitivity From Fasting Insulin and Glucose

No need for log transformation but beware of limits of validity

In recent issues of *Diabetes Care*, 2 articles confirm the concordance between the homeostasis model assessment

insulin resistance index (HOMA-IR) and insulin sensitivity (SI) measured with either the glucose clamp (1) or the minimal model (2). In addition, both indicate that the relationship between HOMA-IR and SI is nonlinear and fits better with an exponential curve (1,2). Accordingly, Fukushima et al. (2) propose to use $\ln(\text{HOMA-IR})$ rather than HOMA itself as a measurement of insulin resistance. Evidence supporting the accuracy of these alternative evaluations of SI from baseline insulin (I) and glucose (G) levels (1–4) appears to be more and more convincing. However, a recent large-scale study shows that such methods are not precise enough to be recommended for the clinical assessment of SI in individual subjects (5). In addition, it is very surprising that, besides $G \times I$ expressed either as a HOMA-IR equal to $G \times I/22.5$ (3) or a fasting insulin resistance index, which is equal to $G \times I/25$ and thus almost equivalent (4), other indexes based on the ratio $G:I$ are also reported to fairly correlate with SI (6). The physiological basis for these indexes is the feedback homeostatic loop between SI and I (7) that is described by the relationship: $SI \times I = a$ (constant). This implies that, unless this homeostatic loop is broken, there is a simple hyperbolic relationship between SI and I as follows: $SI = a/I$. Therefore, SI is proportional to I^{-1} . It is logical to assume that G should also be included in the formula for predicting SI, but whether the best predictor of SI is I/G , $I \times G$, or another formula with the general form $SI = aI^bG^c$ is not clear. After testing different empiric relationships (general form $SI = aI^bG^c$) in 7 distinct samples of subjects in comparison with the minimal model, we found that an index $SI = a/I$ based on the concept of $SI \times I = \text{constant}$ (with $a = 40$ if SI units are $\text{min}^{-1}/(\mu\text{U/ml}) \times 10^{-4}$) was actually the best predictor of SI (8). Thus, we proposed $SI = 40/I$ as a simplified evaluation of SI (9).

Two things remain unclear: 1) which index (HOMA-IR, $\ln[\text{HOMA-IR}]$, G/I , or $40/I$) fits better with minimal model SI, and 2) what are the limits of validity of this alternative measurement of SI?

We measured SI with the minimal model in 68 obese patients (36.25 ± 1.66 years, BMI 34.8 ± 0.7); 44 with type 2 diabetes (53.7 ± 1.8 years, BMI 28.2 ± 0.87); 27 patients explored for reactive hypoglycemia (37.1 ± 3.3 years, BMI 23.1 ± 1.3); 57 athletes (28.6 ± 1.6 years, BMI 22.5 ± 0.28); and 20 lean control subjects (25.73 ± 2.6 years, BMI 20.9 ± 0.6). Correlations of SI with these indexes are shown on Table 1. A step-wise regression analysis chose $40/I$ as the best correlate of SI in obese and type 2 diabetic patients. Mean differences between SI and $40/I$ were as follows: $1.8 \pm 0.12 \text{ min}^{-1} \times 10^{-4} (\mu\text{U/ml})$ (obese), 2.15 ± 0.34 (type 2 diabetic patients), 6.9 ± 0.97 (athletes), and 8.38 ± 3.3 (hypoglycemic patients). These results show that 1) log-transformed HOMA-IR correlates well to SI, but not better than the simpler indexes $40/I$ or G/I ; 2) these simple indexes calculated from I and G poorly correlate with SI in type 2 diabetic patients and do not correlate at all in hypoglycemic patients and athletes.

Therefore, we agree with Bonora et al. (1) and Fukushima et al. (2) that HOMA-IR may provide a good prediction of SI, but we want to point out that log transformation is not necessary because the exponential-like shape of the relationship between SI and I is likely to reflect the homeostatic relationship ($SI = a/I$) rather than an until-now-unreported exponential law. As shown on Table 1, $1/(\text{HOMA-IR})$ correlates at least as well as $\ln(\text{HOMA-IR})$. In addition, in all of the series we have studied, G does not improve the prediction of SI, so that we suggest the index $SI = 40/SI$ as a simple and accurate prediction of SI. It is also very important to emphasize that all of these indexes lose their validity when the feedback loop between SI and I is disturbed (i.e., in major β -cell defects such as overt

Table 1—Correlation coefficients between SI (minimal model) and alternative indexes of insulin sensitivity

	40/I	HOMA-IR	I/G	G/I	$\ln(\text{HOMA})$	1/HOMA	1/ $\ln(\text{HOMA})$
Obese	0.668*	−0.435*	−0.510*	0.639*	−0.580*	0.659*	0.251
Obese + lean	0.343*	−0.277*	−0.342*	0.346*	−0.491*	0.516*	0.189
Type 2 diabetic patients	0.363†	−0.13 (NS)	−0.16 (NS)	0.24 (NS)	−0.177 (NS)	0.213 (NS)	0.083 (NS)
Hypoglycemic patients	−0.02 (NS)	−0.13 (NS)	−0.03 (NS)	0.07 (NS)	−0.074 (NS)	−0.069 (NS)	0.075 (NS)
Athletes	0.11 (NS)	−0.20 (NS)	−0.08 (NS)	0.07 (NS)	−0.218 (NS)	0.221 (NS)	−0.257 (NS)

* $P < 0.001$; † $P < 0.05$.

diabetes or when SI values are high [athletes and reactive hypoglycemia]). Thus, these indexes should be used only in populations in whom their validity has been demonstrated (e.g., nondiabetic obese patients). Outside of these conditions, caution is surely required (5) and there remains a need for other simple validated indexes.

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Assessment of Insulin Sensitivity

Comparison between simplified evaluations and minimal model analysis

There is a need to have a simple index of insulin sensitivity that provides a good correlation with the standard methods as glucose clamp or minimal model analysis (MINMOD) for diabetic patient clinics and large population studies. Fasting insulin (I) and insulin-resistance index assessed by homeostasis model assessment (HOMA-IR), defined as the product of fasting plasma insulin and glucose divided by 22.5, are simplified tools to estimate insulin sensitivity (1–3). Raynaud et al. (4) clarified 40/I as a good evaluation. Emoto et al. (5) and Bonora et al. (6) demonstrated that HOMA-IR and log-transformed HOMA (ln[HOMA]) provided good correlations with the insulin sensitivity index in recent clamp studies. In the present study, we applied MINMOD to compare the estimates of insulin sensitivity

(SI) with various simplified evaluations (7,8). The statistical analysis was performed with the StatView 5 system (Berkeley, CA).

We examined 71 Japanese subjects with normal glucose tolerance (NGT) and type 2 diabetic subjects to assess insulin sensitivity (33.5 ± 1.6 years of age, BMI 20.3 ± 0.33 kg/m²). There were 46 subjects with normal glucose tolerance (27.7 ± 1.3 years of age, BMI 19.9 ± 0.42 kg/m²) and 25 patients with type 2 diabetes (44.4 ± 2.6 years of age, BMI 21.1 ± 0.49). Correlation coefficients and *P* values of the simplified evaluations with MINMOD-derived SI are shown in Table 1. There was a significant correlation between SI in 40/I, HOMA-IR, ln(HOMA), I, 1/HOMA, the ratio of fasting insulin to glucose (I/G), and the ratio of fasting glucose to insulin (G/I). Among them, 40/I, HOMA-IR, ln(HOMA), and I correlated well with MINMOD SI in both NGT and type 2 diabetic subjects. These simple indexes are considered good surrogates for insulin sensitivity estimation. Correlation coefficients of HOMA-IR and ln(HOMA) were higher than 40/I and I in NGT, type 2 diabetes, and all subjects in this study (Table 1). Raynaud et al. (4) demonstrated that 40/I is the best evaluation compared with I, I/G, and HOMA-IR. The reason for the difference between the studies is not known, but it may be in the ethnic differences or clinical characteristics of the subjects examined. Banerji and Lebovitz (9) described 2 subpopulations of type 2 diabetic patients: one with normal insulin sensitivity, and the other with insulin resistance. Arner et al. (10) reported that type 2 diabetic patients with abdominal obesity displayed peripheral insulin resistance, whereas nonobese diabetic patients

Table 1—Comparison of simple indexes with MINMOD-derived SI

	40/I	HOMA-IR	ln(HOMA)	I	I/HOMA	I/G	G/I
All							
<i>r</i>	0.509	0.529	0.577	0.487	0.558	0.311	0.283
<i>P</i>	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.01	<0.05
NGT							
<i>r</i>	0.518	0.531	0.541	0.507	0.523	0.449	0.471
<i>P</i>	<0.0005	<0.0001	<0.0001	<0.0005	<0.0005	<0.005	<0.005
Type 2 diabetes							
<i>r</i>	0.516	0.557	0.547	0.523	0.483	0.391	0.412
<i>P</i>	<0.01	<0.005	<0.005	<0.01	<0.05	0.053 (NS)	<0.05

Data are correlation coefficients and *P* values.