



## 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*

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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 (1) 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  $\text{min}^{-1}/(\mu\text{U}/\text{ml}) \times 10^{-4}$ ) 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[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 ( $36.25 \pm 1.66$  years, BMI  $34.8 \pm 0.7$ ); 44 with type 2 diabetes ( $53.7 \pm 1.8$  years, BMI  $28.2 \pm 0.87$ ); 27 patients explored for reactive hypoglycemia ( $37.1 \pm 3.3$  years, BMI  $23.1 \pm 1.3$ ); 57 athletes ( $28.6 \pm 1.6$  years, BMI  $22.5 \pm 0.28$ ); and 20 lean control subjects ( $25.73 \pm 2.6$  years, BMI  $20.9 \pm 0.6$ ). 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),  $2.15 \pm 0.34$  (type 2 diabetic patients),  $6.9 \pm 0.97$  (athletes), and  $8.38 \pm 3.3$  (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.

40/I	HOMA-IR	I/G	G/I	ln(HOMA)	1/HOMA	1/ln(HOMA)
0.668*	-0.435*	-0.510*	0.639*	-0.580*	0.659*	0.251
0.343*	-0.277*	-0.342*	0.346*	-0.491*	0.516*	0.189
0.363†	-0.13 (NS)	-0.16 (NS)	0.24 (NS)	-0.177 (NS)	0.213 (NS)	0.083 (NS)
-0.02 (NS)	-0.13 (NS)	-0.03 (NS)	0.07 (NS)	0.074 (NS)	-0.069 (NS)	0.075 (NS)
0.11 (NS)	-0.20 (NS)	-0.08 (NS)	0.07 (NS)	-0.218 (NS)	0.221 (NS)	-0.257 (NS)

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

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 [beta]-cell defects such as overt 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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