COMMENTS AND RESPONSES

New Insights on the Simultaneous Assessment of Insulin Sensitivity and β-Cell Function With the HOMA2 Method

Response to Nagasaka et al.

We are very grateful to Nagasaka et al. (1) for their letter addressing relevant issues concerning the joint use of the homeostasis model assessment (HOMA)2 indexes (2,3). Nagasaka et al. measured the HOMA2 indexes of insulin sensitivity (HOMA-S%) and β-cell function (HOMA-B%) in 295 Japanese normal glucose tolerant men. They calculated the natural logarithm of the two indexes and used simple linear regression to analyze the relationship between the log-transformed indexes: $\ln(\text{HOMA-B\%}) = a - b \times \ln(\text{HOMA-S\%})$. They found that the slope b was significantly lower than 1 and concluded that in their dataset the relationship between the HOMA2 indexes was not hyperbolic, but linear. We have two comments to their observations.

First, we agree that when the slope is significantly different from 1, the relationship between the HOMA2 indexes is not hyperbolic. However, this does not necessarily imply that it is linear, as Nagasaka et al. appear to contend. Actually, the relationship between the HOMA2 indexes is $(\text{HOMA-B\%}) \times (\text{HOMA-S\%})^b = e^a$, where "e " is the exponential function. This is not a linear, but a power function. As discussed in ref. 4, a power function is well suited to describe the curvilinear profiles that the indexes of β-cell function and insulin sensitivity often exhibit when they are plotted together (for $b = 1$ the power function coincides with the hyperbolic function). Using the values $a = 7.33$ and $b = 0.592$ estimated by the Japanese investigators, we found a profile that looked definitely curvilinear when plotted on the cartesian plane HOMA-B% versus HOMA-S%. Thus, our interpretation of the findings of Nagasaka et al. is that the relationship between the HOMA2 indexes is curvilinear, albeit not truly hyperbolic, in Japanese normal glucose tolerant subjects.

Our second comment to the letter of Nagasaka et al. concerns the methodology used to analyze the relationship between the log-transformed indexes. We are afraid that simple linear regression is insufficient to reliably estimate the slope and its confidence limits. Simple linear regression assumes that random error only affects the dependent variable and that such error has constant variance. However, in the case of the HOMA2 indexes, it is not clear which index should be treated as the independent variable and which as the dependent. In addition, both HOMA-B% and HOMA-S% are affected by measurement errors, and these errors (originating from the fasting glucose and insulin measurement errors) probably have nonconstant variance. There is another complication. The errors associated to HOMA-B% and HOMA-S% are correlated, and this must be taken into account in the regression analysis by calculating the error variance-covariance matrix. Unfortunately, this calculation is not straightforward because the HOMA2 indexes are not derived from glucose and insulin data by using explicit formulas like the HOMA1 indexes. Monte Carlo techniques can be used to tackle this difficulty. Because common statistical packages are not suited to deal with all these intricacies, we are in the process of developing an appropriate procedure that will hopefully be the subject of a future publication. This will allow us to clarify whether the relationship between the HOMA2 indexes is truly hyperbolic in Italian subjects.

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