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

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The homeostasis model assessment (HOMA) is a method for assessing β-cell function and insulin sensitivity that has gained widespread use thanks to its simplicity and validity (1). The method has recently been reviewed by the group of investigators that championed its development (2). They pointed out that β-cell function cannot be interpreted without the knowledge of insulin sensitivity, and, thus, HOMA of insulin sensitivity (HOMA-S%) should always be reported alongside HOMA of β-cell function (HOMA-B%). Unfortunately, and more often than not, the HOMA indexes are not calculated in tandem. In fact, Wallace et al. (2) observed that in 75% of articles adopting the HOMA method, only HOMA-S% was reported. This is disappointing, since evidence has been accumulating that insulin sensitivity and β-cell function are inextricably linked and should be measured simultaneously because their interplay is fundamental to glucose tolerance. In 1979, Turner et al. (3) disclosed the existence of a curvilinear relationship between the indexes of insulin resistance and β-cell deficiency, which was estimated with a mathematical model of the glucose-insulin feedback loop (a precursor of the HOMA method). In 1981, Bergman et al.(4) showed the presence of a similar relationship between the indexes of insulin sensitivity and β-cell function obtained from the intravenous glucose tolerance test with the minimal model. They also introduced the disposition index (DI), the product of insulin sensitivity times β-cell function, showing that this summary measure was associated with the glucose tolerance displayed during the intravenous glucose tolerance test. These concepts were thoroughly analyzed by Kahn et al. (5), who showed that when insulin sensitivity and secretion are plotted together, a hyperbolic relationship can be observed in healthy humans of varying degree of obesity. Since graphical representation and DI have received considerable attention in recent years (6–10), we thought that they could be profitably applied to the HOMA method. In the following, we report some observations supporting the view that the joint use of HOMA indexes enhances the appeal of HOMA method.

RESEARCH DESIGN AND METHODS

— The HOMA indexes were calculated in 76 normoglycemic nonobese and obese subjects, 15 newly diagnosed diabetic subjects, and 13 obese subjects before and after treatment (diet plus rosiglitazone) (11). The DI, which reflects the overall homeostatic ability of an individual, was also calculated by multiplying HOMA-S% by HOMA-B%. The HOMA indexes were calculated using the updated HOMA2 method (based on the computer model) because it is more accurate than the original HOMA1 method (based on explicit formulas) (2). Results are expressed as median values (interquartile range).

RESULTS

— In Fig. 1, we plotted individual HOMA indexes measured in normoglycemic subjects and median HOMA indexes measured in diabetic subjects, as well as in the obese patients, before and after therapy. By looking at the diagram, it can be seen that the combined use of the HOMA indexes makes it easier for investigators to determine the relative importance of insulin-sensitive tissues and the pancreas to carbohydrate metabolism. For instance, obese subjects appear to compensate for their insulin resistance with a higher β-cell responsivity. In contrast, diabetic subjects are not able to accomplish such compensation, and this is confirmed by their position on the diagram (the DI of the diabetic group is half that of nondiabetic subjects, 0.41 vs. 1.04, respectively). The improvement in the metabolic status of the obese group after therapy is mirrored by a shift on the diagram toward a region characterized by higher insulin sensitivity, lower insulin secretion, and higher DI (DI changes from 0.91 to 1.33).

CONCLUSIONS

— Our observations suggest that the joint representation of the HOMA indexes has the potential to reveal facets of the metabolic status of an individual that might not otherwise be apparent, to better characterize differences between groups, and to monitor the effect of therapies. It is worthwhile to discuss the finding that the HOMA scatter plot is reminiscent of the hyperbolic relationship previously reported by Kahn et al. (5). Such curvilinear shape means that changes in HOMA-S% tend to be compensated by reciprocal changes in HOMA-B%; thus, DI remains approximately constant. Why are the HOMA indexes able to reproduce such a peculiarity of the glucose system? To answer this question, we can derive DI using the original HOMA1 formulas, which, albeit are approximated, make explicit the contributions of basal glucose (G_b) and basal insulin (I_b). Given that HOMA1-S (insulin sensitivity) = $22.5/G_bI_b$ and HOMA1-B (β-

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Abbreviations: DI, disposition index; HOMA, homeostasis model assessment; HOMA-B%, HOMA of β-cell function; HOMA-S%, HOMA of insulin sensitivity.

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

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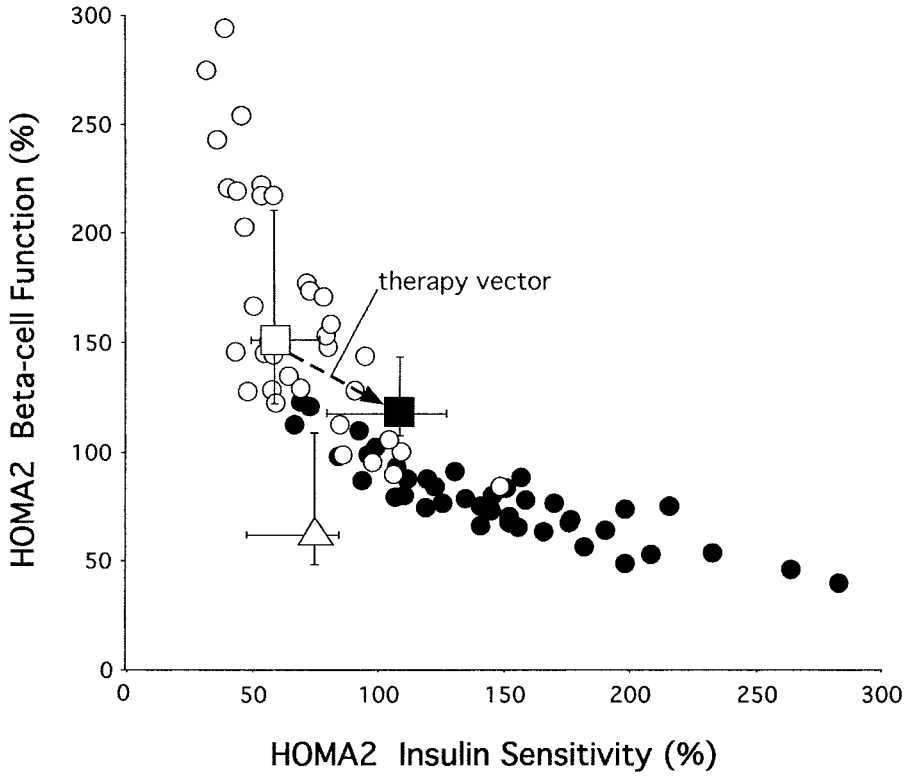

Figure 1—*Relationship between HOMA-S% and HOMA-B% measured with the HOMA2 method. Individual HOMA indexes measured in a group of 76 normoglycemic subjects (41 nonobese subjects [●] with median BMI = 20.7 kg/m^2 [interquartile range 19.0–23.0] and G_b = 89.7 mg/dl [87.0–92.8]; and 35 obese subjects [○] with BMI = 40.9 kg/m^2 [39.1–43.1] and G_b = 81.0 mg/dl [75.8–88.0]). Median (interquartile range) of the HOMA indexes were calculated in a group of 15 newly diagnosed diabetic subjects (△) with G_b = 129.5 (99.8–145.7) and a group of 13 normoglycemic obese subjects before (□) (BMI = 42.1 kg/m^2 [40.1–44.9] and G_b = 85.0 [79.0–88.0]) and after (■) (BMI = 37.0 kg/m^2 [35.9–39.8] and G_b = 79.0 [77.5–83.0]) a treatment comprising diet and administration of rosiglitazone (11).*

cell function) = $20I_b/(G_b - 3.5)$, then DI = $450/[G_b(G_b - 3.5)]$, which is a function of basal glucose only (this is an approximation because the HOMA2 DI also depends on insulin). Because the range of basal glucose levels in normoglycemic subjects is narrow (thanks to a healthy homeostatic system), DI does not vary much among them and the scatter plot takes on a quasi-hyperbolic shape. The observation that a curvilinear relationship between insulin sensitivity and β-cell function is virtually built in the HOMA method is not new (12) and is not necessarily disappointing. Rather, it may be additional evidence that the HOMA method encapsulates the basic features of the glucose-insulin feedback loop, as pointed out by Radziuk (13). In particular, the interpretation of the HOMA-based DI as an index of glucose tolerance is corroborated by the fact that G_b, which plays the key role in DI, is a good predictor of oral glucose tolerance (14). On the other hand, it must be kept in mind that the HOMA indexes are based on an oversimplified model that exploits basal data to infer metabolic processes that are fully disclosed only when the glucose system is challenged by an exogenous perturbation. This certainly limits the accuracy with which they surrogate the relationship between insulin sensitivity and β-cell function. Thus, validation studies of the joint use of the HOMA indexes against more elaborate approaches are warranted.

In conclusion, the combined representation of the HOMA-S% and HOMA-B% has the potential to provide meaningful insights into glucose metabolism, both at the individual and at the group level. This motivates further research to define the domain of validity of the joint use of the HOMA indexes with respect to more elaborate approaches.

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