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SHORT COMMUNICATION

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Comparative evaluation of simple insulin sensitivity methods based on the oral glucose tolerance test

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Abstract *Aims/hypothesis:* We compared five surrogate insulin sensitivity (IS) methods against the euglycaemic–hyperinsulinaemic clamp. These methods were the homeostasis model assessment (HOMA) and four methods based on the OGTT (OGIS, MCRest, ISIcomp, SIORAL). *Methods:* We compared these IS methods against the clamp (0.28 nmol·min^{-1}·m^{-2} insulin infusion) *M* value in 147 women (58–61 years; BMI 19–38 kg/m^2; 116 NGT, 25 IFG/IGT, six type 2 diabetic), by evaluating the correlation coefficient with *M*. We also tested the ability to reproduce the relationships between IS and typical IS correlates (BMI, fasting insulin, insulin to glucose OGTT area ratio and fasting, 2 h and mean glucose) by means of the "discrepancy index" *D*, in which (1) $D=0$ if the correlation between IS and the variable of interest is as with the clamp, (2) *D* is smaller than 0 if the correlation is overestimated, and (3) *D* is greater than 0 if underestimated. *Results:* All IS methods correlated with *M* ($r=0.57$–0.83, $p<0.0001$); for MCRest the relationship was markedly curvilinear. All IS measures correlated with the considered variables ($r=0.29$–0.94, $p<0.0005$); however, no method had $D\approx0$ for all variables. The best surrogates of *M* were OGIS (one $D\neq0$) and MCRest (two $D\neq0$); the other methods either under- or overestimated the degree of correlation (three or more $D\neq0$), in particular with fasting insulin (HOMA: $D=-57\%$; ISIcomp: $D=-36\%$) and BMI (HOMA: $D=-14\%$; ISIcomp: $D=-14\%$; SiORAL: $D=-11\%$). *Conclusions/interpretation:* All IS methods were correlated with *M*. OGIS and MCRest were preferable to the other methods and in particular to HOMA for reproducing relationships with the independent variables.

Keywords Glucose clamp · Glucose tolerance · Insulin sensitivity · OGTT

Abbreviations BW: Body weight · D: Discrepancy index · HOMA: Homeostasis model assessment · IS: Insulin sensitivity · SISI: Surrogate insulin sensitivity index

Introduction

The investigation of the pathophysiology of the metabolic syndrome and type 2 diabetes requires a valid insulin sensitivity index, in particular when associations between insulin sensitivity and other metabolic characteristics, such as insulin secretion, are examined, e.g., as in Ref. [1]. The difficulty of performing a euglycaemic–hyperinsulinaemic clamp in large studies has stimulated the use and development of surrogate insulin sensitivity indices (SISIs), from the simplest homeostasis model assessment (HOMA) methods to the more elaborate OGTT-based methods [2].

Although SISIs have been validated against the clamp, a comparative evaluation on an independent database is not available. Furthermore, validity has mostly been limited to correlation tests with the clamp. The aim of this study was to provide such a comparative evaluation; in addition, we evaluated the ability of SISIs to reproduce classical relationships between insulin sensitivity and some typical insulin sensitivity correlates such as obesity, insulin secretion parameters and glucose tolerance. The latter test is particularly important in view of the pathophysiological relevance of these relationships.

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Subjects and methods

Experimental procedures After an overnight fast, we performed on separate days a euglycaemic (~5 mmol/l glucose) hyperinsulinaemic (0.28 nmol/min per m^2 body surface area insulin infusion) glucose clamp [3] and a standard 75-g OGTT on 147 postmenopausal women. Sampling for glucose and insulin in the OGTT was at 0, 30, 60, 90, 120 min. The subject characteristics were 116 NGT, 25 IFG/IGT, six type 2 diabetic (ADA 2002 criteria); age 58 to 61 years old; BMI 26±0.3 kg/m^2. The subjects had been previously recruited for other studies [3]. The study was approved by the Lund University ethics committee and the subjects gave written informed consent.

Insulin sensitivity indices The clamp *M* value (mg·min^{-1}·kg body $weight^{-1}$) was calculated as the mean glucose infusion rate during the last 60 min. HOMA [4] was calculated as the product of glucose and insulin concentrations in the first (basal) OGTT sample. As HOMA is an insulin resistance index logarithmically related to *M* value, insulin sensitivity from HOMA was expressed as HOMAinv=1/logHOMA [2]. The three most extensively validated OGTT IS indices were considered, i.e., Matsuda and DeFronzo (ISIcomp [5]), Stumvoll et al. (MCRest [6]), Mari et al. (OGIS [7]). In addition, the minimal model based index by Caumo et al. (SiORAL [8, 9]) was tested. As most of the OGTT indices have been validated against a clamp index normalised to body weight (BW), for homogeneity the original units of OGIS (ml/min per m^2 body surface area) were converted to mg·min^{-1}·kg BW^{-1}.

Typical insulin sensitivity correlates We examined the relationships between SISIs and BMI, fasting insulin (marker of fasting insulin secretion), the ratio of insulin to glucose areas under the OGTT concentration curves (index of glucose-stimulated insulin secretion), fasting glucose, 2-h glucose and mean glucose concentration during the whole OGTT. We did not consider the insulinogenic index [2], which yielded numerous negative or very large outliers. C-Peptide was not available to compute true insulin secretion.

Statistical analysis Standard linear regression was used for correlations. Logarithmic transformations were used to linearise the relationships, if necessary. A *p* value of less than 0.05 was considered statistically significant. To evaluate the ability of SISIs to accurately represent the relationships between IS and the other variables, we calculated a discrepancy index (*D*), defined as $D=SD_{sisi}/SD_{clamp}-1$, where SD_{sisi} is the SD of residuals of the regression of the variable of interest against SISI under consideration; SD_{clamp} is the corresponding SD for the *M* value. If *D* is not significantly different from 0, clamp and SISI exhibit the same degree of correlation with the variable of interest, i.e., an equal SD of the regression residuals; the degree of correlation is overestimated if *D* is less than 0, and underestimated if *D* is greater than 0. The absolute value of *D* gives the degree of over- or underestimation.

To test whether *D* was significantly different from 0, we used a permutation test; a similar approach was used previously [10]. In short, the null distribution was estimated by permuting the residuals of the two regression lines to be compared on a case-by-case basis. This is justified because if the *M* value and SISI correlate in the same way with the variable of interest (e.g., fasting insulin), the residual obtained for a particular subject with one index is exchangeable with the residual obtained with the other index. The reported two-sided *p* values were based upon a random subsample of 5,000 permutations, and were calculated as the percentage of simulated *D* values that in absolute value were larger than the absolute value of the given discrepancy index.

Results

Table 1 shows the correlation coefficients between *M* values and SISIs. The relationships were from virtually linear (ISIcomp) to markedly curvilinear (MCRest), as also indicated by the improvement in the correlation coefficient after logarithmic transformation. Notably, MCRest was better correlated with the logarithm of *M*, i.e., MCRest is an estimate of log*M*. MCRest yielded negative values of insulin sensitivity in the three most insulin-resistant subjects.

The correlation coefficients between *M* values and the typical IS correlates were −0.60 for BMI, −0.63 for fasting insulin, −0.29 for OGTT insulin to glucose ratio, −0.65 for mean glucose, −0.46 for fasting glucose and −0.58 for 2-h glucose ($p<0.0005$, after log transformation). Significant correlations of various degrees between these variables and all SISIs were also observed (after log transformation of variables except MCRest, which is an estimate of log*M*).

The ability of SISIs to reflect these relationships accurately was quantified by the discrepancy indices (*D*) shown in Fig. 1a. An accurate method would have yielded $D\approx0$ for all methods; this happened for no SISI. OGIS had the lowest number of nonzero *D*'s (one *D*), followed by MCRest (two *D*'s), and then by the other methods. It is of particular relevance that ISIcomp, SiORAL and HOMAinv overestimated the degree of correlation with the insulin secretion parameters.

Figure 1b illustrates the significance of a nonzero *D* on the analysis of the relationship between IS and fasting in-

Table 1 Correlation coefficients between the glucose clamp *M* value and the surrogate insulin sensitivity methods, with or without logarithmic transformation of the variables

Method	Untransformed variables	Transformed variables
OGIS	0.67	0.73
MCRest	0.69	0.83[a]
ISIcomp	0.71	0.73
SiORAL	0.68	0.75
HOMAinv	0.57	0.65[b]

[a]Log transformation only for *M*, as MCRest is an estimate of log*M*
[b]Correlation coefficient between logHOMA and log*M* was −0.67.
All correlations were highly significant ($p<0.0001$)

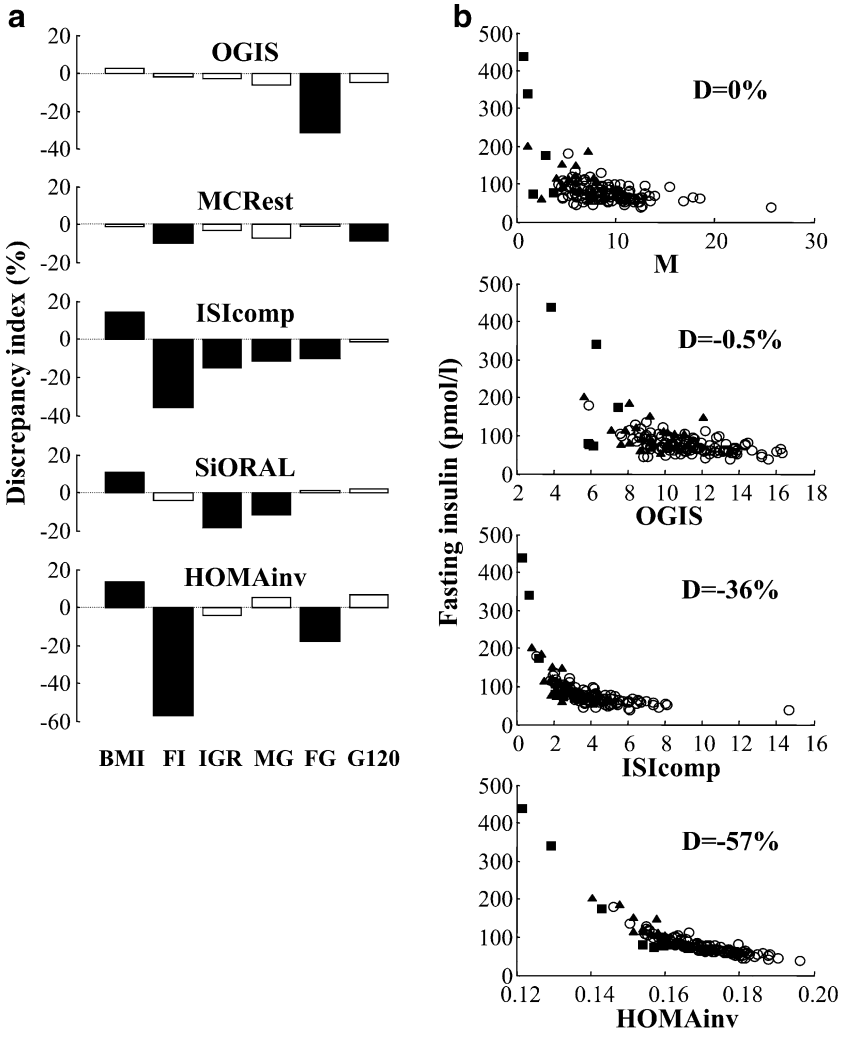

Fig. 1 Discrepancy indices (*D*) expressing the appropriateness of the representation of the relationships between insulin sensitivity (*IS*) and typical IS correlates. **a** *D* values for all surrogate IS methods, relative to the relationships between IS and BMI, fasting insulin (*FI*), OGTT insulin to glucose area ratio (*IGR*), mean glucose (*MG*), fasting glucose (*FG*) and 2-h glucose (*G120*). For an ideal IS method, all *D*'s should be 0. $D>0$ indicates underestimation of the degree of correlation, $D<0$ overestimation. *Black bars* indicate that *D* is statistically different from 0 ($p<0.05$). **b** Significance of a nonzero *D* for the analysis of the relationship between IS and fasting insulin. As *D* becomes increasingly negative, the inverse relationship becomes falsely tighter. While OGIS ($D=-0.5\%$) reproduces the pattern seen with the clamp, ISIcomp and HOMAinv progressively overestimate the degree of correlation ($D=-36\%$ and -57%). *Circles* NGT subjects, *triangles* IFG/IGT subjects, *squares* type 2 diabetic subjects

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Discussion

This study examines for the first time the ability of several SISIs to describe accurately the relationships between insulin sensitivity and some typical insulin sensitivity correlates. We show that although all SISIs are reasonably well correlated with the clamp, as previously reported, they differ in the ability to represent accurately the relationships between IS and typical correlates. In this sense, none of the methods is an unbiased estimate of the *M* value; however, OGIS and MCRest appear to be the IS surrogates closest to the clamp, although MCRest was curvilinearly related to *M* and yielded some negative values. Interestingly, these two methods are to some extent complementary: OGIS is a good substitute for *M* except for the relationship with fasting glucose, which is instead well described by MCRest.

The ability of SISI to represent appropriately the relationship between IS and other variables depends on the equation for estimating IS. If the variable of interest and SISI share the same measurements (such as fasting insulin or the insulin or glucose areas) and these shared data do not have an independent role in the two indices, spurious correlations are likely to arise. This is the case with HOMA and ISIcomp and fasting insulin, or with ISIcomp and mean glucose.

An additional new finding of this study is that OGIS and MCRest have clear advantages over HOMA when describing the relationships between IS and insulin secretion (assessed by fasting insulin) and other variables. This holds even if the OGTT is not better than HOMA in terms of correlation with the clamp. This study thus supports the use of OGTTs rather than HOMA for assessing IS in studies in which an OGTT is feasible, while the clamp or minimal model are not.

An obvious caveat in our analysis is that the ranking of the methods may somewhat depend on the specific database used, as in all other studies of this kind. Furthermore, it should be remembered that the OGTT methods provide surrogates of IS and are not intended to replace more direct approaches such as the clamp or minimal model.

In conclusion, this study supports the use of the OGTT for the assessment of insulin sensitivity from a simple test, and among the tested methods qualifies OGIS and MCRest as the most accurate surrogates of *M* value. These OGTT methods are potentially useful for studies involving a large number of subjects.

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