Assessment of insulin sensitivity and beta-cell function from measurements in the fasting state and during an oral glucose tolerance test

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Abstract

Aims/hypothesis. We aimed to find if the relation between insulin sensitivity and beta-cell function assessed from fasting and OGTT measurements has a physiological shape (hyperbolic with the reference methods).

Methods. Healthy women without diabetic first-degree relatives underwent a 75 g OGTT with plasma glucose and insulin ($n = 35$) concentrations being measured at 0, 30, 60 and 120 min. Beta-cell function and insulin sensitivity were estimated using previously described indices from fasting (1 for beta-cell function, 6 for insulin sensitivity) and OGTT measurements (3 for beta-cell function and 5 for insulin sensitivity). A hyperbolic relation was tested for the 21 beta-cell function-insulin sensitivity pairs using a non-linear regression method.

Results. The assessment of beta-cell function from OGTT was impossible in seven women and one had

outlier indices. For the remaining 27 women, only 8 combinations adjusted to a hyperbolic relation. The best adjustment was achieved using the fasting glucose to insulin ratio as the estimation of insulin sensitivity and the homeostasis model assessment (HOMA) index (single fasting sample) as the estimation of beta-cell function (r^2 0.802, k 869.71, $p < 0.001$).

Conclusion/interpretation. In this group of healthy women, the estimation of insulin sensitivity and beta-cell function by most methods using OGTT-derived glucose and insulin measurements did not adjust to a hyperbolic relation but all fasting indices combinations did. Beta-cell function estimated with the HOMA index and insulin sensitivity with fasting glucose to insulin ratio had the best adjustment. [Diabetologia (2000) 43: 1507–1511]

Keywords Insulin sensitivity, OGTT, Beta-cell function, insulin secretion.

The gold-standard methods to assess insulin sensitivity (IS) and beta-cell function are time-consuming and difficult to use in large-scale clinical or epidemiological studies where simpler methods are required. This has raised interest in obtaining estimates from glucose and insulin measured in the fasting state or dur-

ing an OGTT. Several indices of beta-cell function and IS obtained from fasting and OGTT measurements have been described and most of them have been validated with reference methods [1–4]. The aim of our study was to examine if the relation between IS and beta-cell function assessed from fasting and OGTT measurements with these simple indices keeps the physiological relation that for the reference methods has been described to be hyperbolic. In 1993, a study showed that the lower the IS the higher the insulin concentrations and the higher the IS, the lower the insulin concentrations so that the product of beta-cell function and IS is approximately a constant [5]. Other studies have confirmed this relation

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Abbreviations: : IS, insulin sensitivity; HOMA, homeostasis model assessment.

Table 1. Formulas and references of indices of insulin sensitivity and beta-cell function derived from fasting and OGTT measurements of glucose and insulin

Index	Formula	Reference
<i>Beta-cell function indices</i>		
HOMA index	$20 \times \frac{\text{ins}0'}{(\text{glu}0' - 3.5)}$	[1]
Stumvoll index	1 st phase = $1283 + 1.829 \times \text{ins}30' - 138.7 \times \text{glu}30' + 3.772 \text{ ins}0'$	[3]
Insulinogenic index (30')	$\frac{\text{ins}30' - \text{ins}0'}{\text{glu}30' - \text{ins}0'}$	[8]
Insulinogenic index (120')	$\frac{\Delta\text{AUC ins}}{\Delta\text{AUC glu}}$	[9]
<i>Insulin sensitivity indices</i>		
Fasting insulin ⁻¹	$\frac{1}{\text{ins}0'}$	[10]
Fasting glucose to insulin ratio	$\frac{\text{glu}0'}{\text{ins}0'}$	[11]
HOMA index	$\text{IR} = \frac{\text{ins}0'}{22.5e^{-\text{Ln glu}0'}} \quad \text{IS} = \frac{1}{\text{IR}}$	[1]
Raynaud index	$\frac{40}{\text{ins}0'}$	[12]
Fasting Belfiore index	$\frac{2}{(\text{ins}0' \times \text{glu}0') + 1}$	[13]
FIRI ⁻¹	$\text{FIRI} = \frac{\text{glu}0' \times \text{ins}0'}{25} \quad \text{FIRI}^{-1} = \frac{1}{\text{FIRI}}$	[14]
Insulin 120 min ⁻¹	$\frac{1}{\text{ins}120'}$	[3]
AUCglu-AUCins OGTT ratio	$\frac{\text{AUCglu}}{\text{AUCins}}$	[9]
Cederholm index	$\frac{\text{MCR}}{\log\text{MSI}} = \frac{M}{\text{MBG}/\log\text{MSI}}$	[15]
Matsuda index	$\frac{10000}{\sqrt{(\text{glu}0' \times \text{ins}0') (\text{mean gluOGTT} \times \text{mean insOGTT})}}$	[2]
OGTT-Belfiore index	$\frac{2}{(\text{AUC ins} \times \text{AUC glu}) + 1}$	[13]

glu: glucose, ins: insulin, IS: insulin sensitivity, IR: insulin resistance,

FIRI: fasting insulin resistance index, MCR: metabolic clearance rate, ln: natural logarithm, MSI: mean serum, MBG: mean blood glucose, *M*: peripheral glucose uptake rate

between IS and beta-cell function [6] but some investigators describe a negative association although they did not test for a hyperbolic relation [7].

Subjects and methods

The study was done in the context of a larger investigation of gestational diabetes mellitus, where control women were studied to have reference values for beta-cell function and IS. Healthy women ($n = 35$) with normal glucose tolerance participated in the study after signing an informed consent. The pro-

cedure was carried in accordance with the principles of the Declaration of Helsinki as revised in 1996. All women were Caucasian and younger than 35 years of age. Mean age was 29.8 ± 2.9 years and mean body mass index was 22.6 ± 3.2 kg/m². None of them had first-degree relatives with diabetes mellitus. A 75-g OGTT was done after 3 days on a 2000-kcal diet and after a 12-h overnight fast. Glucose was measured with a glucose-oxidase method (Technicon RA-Xt analyzer, Terry Town, Mont., USA). Insulin was measured by an immunoradiometric assay (Biosource Europe, Nivelles, Belgium) without cross-reactivity with proinsulin. Intra-assay CVs were 4.5 and 2.1% at mean concentrations of 47 and 380 pmol/l and inter-assay CV were 12.2 and 4.7% at mean concentrations of 70 and 259 pmol/l. To estimate beta-cell function and IS we used

Fig 1. Relation between insulin secretion (estimated as single fasting sample HOMA index) and insulin sensitivity (estimated as glucose to insulin ratio). The relation adjusts to a hyperbolic curve (k 869.71, r^2 0.802, $p < 0.001$).

all described indices derived from either fasting or OGTT (0, 30, 60, 120 min) measurements of glucose and insulin (Table 1). Beta-cell function was estimated in the fasting state with the homeostasis model assessments (HOMA) index and during the OGTT with the Stumvoll index and with the insulinogenic index during the first 30 min or during the entire OGTT. The IS was estimated in the fasting state with reciprocal fasting plasma insulin, fasting glucose to insulin ratio and HOMA, Raynaud, fasting-Belfiore and reciprocal fasting insulin resistance indices. The IS during OGTT was estimated with reciprocal 120-min plasma insulin, OGTT AUC-glucose to AUC-insulin ratio and Cederholm, Matsuda and OGTT-Belfiore indices. The HOMA indices were calculated using the mathematical estimation in a single fasting sample. For each test, glucose and insulin were expressed using the units of the original description. For indices of insulin resistance (i.e. FIRI), the reciprocal value was used for the analysis of the relation with beta-cell function.

Statistical analysis was done with a SPSS for Windows 8.0 package. Quantitative variables are expressed as means $\pm$ SD. Because fasting and postload indices probably measure different aspects of glucose homeostasis, we grouped beta-cell function and IS indices according to their fasting or postload nature. A hyperbolic relation was tested for the 21 combinations of IS and beta-cell function pairs using a non-linear regression method and analysing if the two variables followed a model defined by beta-cell function = K/IS . The initial K was the product of IS by beta-cell function in the group studied. The best adjustment to a hyperbolic curve was searched, with iterations being stopped when the magnitude of the largest correlation between the residuals and any derivative column was at most 1.10^{-8} . The fitting to a hyperbolic relation was considered to be significant if the r^2 corresponding to the best adjustment was significant at a $p < 0.0024$ ($p < 0.05$ with a Bonferroni correction for 21 comparisons).

Results

The assessment of beta-cell function from OGTT (insulinogenic index during the first 30 min or the entire OGTT) was impossible in seven women (infinite or negative values) and yielded clear-cut outlier indices in one. Estimation of beta-cell function in the remaining 27 women were as follows: HOMA index $89.9 \pm 50.1\%$, Stumvoll index $1306.1 \pm 591.4 \text{ pmol} \cdot \text{l}^{-1}$, insulinogenic index during the first 30 min $24.4 \pm 21.2 \text{ mU} \cdot \text{mmol}^{-1}$ and insulinogenic index during the entire OGTT $2.89 \pm 2.88 \cdot 10^{-4} \text{ UI} \cdot \text{mg}^{-1}$. Indices of IS were: reciprocal fasting plasma insulin $0.13 \pm 0.05 \text{ mUI}^{-1} \cdot \text{l}$, fasting glucose to insulin ratio $11.3 \pm 4.1 \cdot 10^4 \text{ UI} \cdot \text{mg}$, HOMA index $120.5 \pm 50.4\%$, Raynaud index $5.25 \pm 2.0 \mu\text{UI}^{-1} \cdot \text{l}$, fasting-Belfiore index $1.01 \pm 0.42 \text{ pmol}^{-1} \cdot \text{l} \cdot \text{mmol}^{-1} \cdot \text{l}$, reciprocal fasting insulin resistance index $0.70 \pm 0.29 \text{ mmol}^{-1} \cdot \text{mUI}^{-1} \cdot \text{l} \cdot \text{l}$, reciprocal 120 min plasma insulin $0.0047 \pm 0.003 \text{ pmol}^{-1} \cdot \text{l}$, OGTT AUC-glucose to AUC-insulin ratio $2.65 \pm 1.28 \cdot 10^4 \text{ U} \cdot \text{mg}$, Cederholm index $63.5 \pm 10.8 \text{ mg} \cdot \text{l} \cdot \text{l} \cdot \text{mmol}^{-1} \cdot \text{mUI}^{-1} \cdot \text{min}^{-1}$, Matsuda index $5.71 \pm 2.07 \cdot 10^{-4} \text{ UI}^{-1} \cdot \text{ml} \cdot \text{mg}^{-1} \cdot \text{ml}$ and OGTT-Belfiore $1.04 \pm 0.44 \text{ pmol}^{-1} \cdot \text{l} \cdot \text{h}^{-1} \cdot \text{mmol}^{-1} \cdot \text{l} \cdot \text{h}^{-1}$. The adjustment to a hyperbolic relation of all beta-cell function and IS pairs is depicted in Table 2. All fasting indices combinations adjusted to a hyperbolic relation (6/6) but only two out of 15 postload indices did. Beta-cell function estimated by HOMA index and IS by fasting glucose to insulin ratio had the best adjustment in this group of women (r^2 0.802, k 869.71, $p < 0.001$) (Fig.1). Among postload indices, Stumvoll index as a measure of beta-cell function and AUC glucose-AUC insulin OGTT ratio achieved the best adjustment to a hyperbolic curve.

Discussion

In the last two decades, several simple indices of beta-cell function and IS have been described and new ones continue to be incorporated. They have been validated against the reference methods but the adjustment of beta-cell function-IS pairs to a hyperbolic relation has not been tested.

In this study, 7 out of 35 women had impossible estimates of beta-cell function with OGTT-derived indices, which is a great drawback to their use. Because the relation beta-cell function-IS was tested after excluding women with either impossible or outlier beta-cell function indices, the study group can be viewed as artificially homogeneous. Nevertheless, only 8 out of 21 beta-cell function-IS pairs fitted a hyperbolic relation, which was unexpected because such a relation was anticipated even if its strength was less than with the reference methods. Because

Table 2. Adjustment to a hyperbolic curve of the relation between indices of insulin secretion and sensitivity derived from fasting and OGTT measurements of glucose and insulin in 27 healthy women. The r^2 value and significance are provided

<i>Fasting indices</i>							
Insulin sensitivity → Insulin secretion ↓	Fasting insulin ⁻¹	Fasting glucose to insulin ratio	HOMA index	Raynaud index	Fasting-Belfiore index	FIRI ⁻¹	Total
HOMA index	0.624 ^a	0.802 ^a	0.386 ^a	0.624 ^a	0.387 ^a	0.386 ^a	6/6
<i>OGTT indices</i>							
Insulin sensitivity → Insulin secretion ↓	Insulin 120 min ⁻¹	AUCG-AUCI OGTT ratio	Cederholm index	Matsuda index	OGTT-Belfiore index		Total
Stumvoll index	0.062	0.685 ^a	0.100	0.365 ^a	0.269		2/5
Insulinogenic index (30')	0.065	0.268	0.057	0.008	0.015		0/5
Insulinogenic index (120')	0.022	0.092	0.131	0.070	0.185		0/5
Total	0/3	1/3	0/3	1/3	0/3		2/15

^a $p < 0.0024$

FIRI: fasting insulin resistance index

the study population was limited to women younger than 35 years, the results cannot be attributed to an age-related impairment of insulin secretion.

The maintenance of a hyperbolic physiologic relation is not a sufficient validation for a beta-cell function or IS index (they have to be validated against the reference methods), but we suggest that it should be an additional one (otherwise, what do the indices represent?).

The results of this study endorse the use of some fasting or OGTT-derived indices of beta-cell function and IS, especially fasting indices which have a physiological relation in all cases. This adds to recent information indicating that simple indices can be similar or superior to gold-standard methods in several aspects. For example, the HOMA-IS index has been reported to have a precision similar to that of the glucose clamp [16] and the HOMA-IS index and reciprocal fasting plasma insulin are similar to minimal model-derived measurements in discriminating subjects with different degrees of glucose tolerance [10]. For beta-cell function, HOMA-beta-cell function offers a discrimination across subjects with normal glucose tolerance, IGT and Type II (non-insulin-dependent) diabetes mellitus which is even better than that derived from IVGTT measurements [17].

In this group of healthy women, the estimation of beta-cell function and IS with several validated indices using fasting or OGTT measurements depicted a hyperbolic relation only in 8 out of 21 combinations. The IS estimated as the fasting insulin to glucose ratio and beta-cell function as the HOMA index had the most physiological relation.

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