

## ASSESSMENT OF INSULIN SENSITIVITY/RESISTANCE IN EPIDEMIOLOGICAL STUDIES

ZOFIA RADIKOVA

*Institute of Experimental Endocrinology, Slovak Academy of Sciences, 833 06 Bratislava, Slovakia*  
e-mail: *Zofia.Cervenakova@savba.sk*

Hyperinsulinemic euglycemic clamp is known to be the “gold standard” in measurement insulin sensitivity. However, its time and financially consuming realization led to a simplified approach in quantification of insulin sensitivity. Various indices of insulin sensitivity/resistance using the data from an oral glucose tolerance test were proposed in last 20 years. The aim of this review is to evaluate critically the use of some of the proposed indices in insulin sensitivity estimation.

There are two groups of insulin sensitivity indices: 1. indices calculated by using fasting plasma concentrations of insulin, glucose and triglycerides, 2. indices calculated by using plasma concentrations of insulin and glucose obtained during 120 min of a standard (75g glucose) oral glucose tolerance test. Some authors used demographic parameters (BMI, age, weight) in their formulas to achieve the best correlation with euglycemic clamp data.

These indices are conveniently used in epidemiological and clinical studies to predict diabetes development in a non-diabetic population. Their use in clinical practice is limited because of the absence of reference values for normal and impaired insulin sensitivity.

**Key words:** Insulin sensitivity index – Oral glucose tolerance test – Insulin – Glucose

### Minireview

Insulin resistance is accepted to be a major risk factor in the etiology of diabetes mellitus Type 2 (LILLIOJA et al. 1993), hypertension, dyslipidemias, atherosclerotic vascular disease (BLOOMGARDEN 1998, GUTT et al. 2000), and may be a risk factor for coronary heart disease (ABBASI et al. 2002) and stroke (KERNAN et al. 2002).

Several risk factors (e.g. obesity, physical inactivity, body fat distribution, age and hyperinsulinemia) may be considered markers of insulin resistance (HARRIS 1995). Insulin resistance is a predictor of diabetes mellitus Type 2 development even in individuals with normal glucose tolerance (LILLIOJA et al. 1993, SICREE et al. 1987, SAAD et al. 1994). Therefore it is important to recognize insulin resistance in the pre-disease stage when therapeutic intervention is likely to be more successful than in manifest disease.

Several authors proposed various indices of insulin sensitivity based on the interrelations between the concentration of insulin, glucose and other parameters obtained either in fasting state or during oral glucose tolerance test (OGTT) and correlated the indices with the data obtained during a hyperinsulinemic euglycemic clamp (HEC) (MATTHEWS et al. 1985, CEDERHOLM and WIBELL 1990, BELFIORE et al. 1998, MATSUDA and DEFRONZO 1999, AVIGNON et al. 1999, KATZ et al. 2000, STUMVOLL et al. 2000, STUMVOLL et al. 2001). The HEC-derived index of insulin sensitivity ( $ISI_{HEC}$ ,  $ml \cdot kg^{-1} \cdot min^{-1} \cdot \mu IU^{-1} \cdot ml$ ) is obtained during a steady state period of HEC (DEFRONZO et al. 1979).

$$ISI_{HEC} = MCR/I_{mean}, \text{ where}$$

$I_{mean}$  – average steady state plasma insulin response ( $\mu IU/ml$ ),

MCR – metabolic clearance rate of glucose (ml.kg<sup>-1</sup>.min<sup>-1</sup>).

$$\text{MCR} = M_{\text{mean}} / (G_{\text{mean}} \times 0.18), \text{ where}$$

$M_{\text{mean}}$  – metabolized glucose expressed as average steady state glucose infusion rate per kg of body weight (mg.kg<sup>-1</sup>.min<sup>-1</sup>)

$G_{\text{mean}}$  – average steady state blood glucose concentration (mmol/l)

0.18 – conversion factor to transform blood glucose concentration from mmol/l into mg/ml

Insulin sensitivity could be assessed by estimation of these indices referring to impairment in insulin sensitivity in individuals with normal glucose tolerance. Correct application of the indices in their proposed form and with the proposed concentration units is of high importance. A modification of the indicated calculations may lead to incoherence of results and to their incomparability with results of other authors.

Therefore, the aim of this review is to introduce several insulin sensitivity indices, their formulas and units as proposed by their authors and to evaluate critically the use of some of the suggested indices in insulin sensitivity estimation.

### IR<sub>HOMA</sub>

Indices of insulin sensitivity/resistance derived from fasting glucose and insulin concentrations reflect hepatic insulin sensitivity and basal hepatic glucose production.

MATTHEWS et al. (1985) proposed a computer model of insulin-glucose interactions called homeostasis model assessment (HOMA). They assumed that normal-weight healthy subjects aged <35 years have 100%  $\beta$ -cell function and insulin resistance of 1. An index of insulin resistance, IR<sub>HOMA</sub>, is the mathematical equivalent of the computer model. Its correlations with estimates obtained by hyperinsulinemic euglycemic clamp (HEC) were reported to be 0.88;  $p < 0.0001$  (MATTHEWS et al. 1985) and -0.59;  $p < 0.0005$  (STUMVOLL et al. 2000). Value of insulin resistance can be assessed from fasting insulin (mIU/l) and glucose (mmol/l) concentrations. MATSUDA and DEFONZO (1999) correlated the inverse value of this index with HEC in subjects with normal glucose tolerance (0.65;  $p < 0.0001$ ), with impaired glucose tolerance

(0.56;  $p < 0.0001$ ) and in patients with diabetes Type 2 (0.51;  $p < 0.0001$ ).

The equation proposed by Matthews et al.:

$$\text{IR}_{\text{HOMA}} = I_0 / (22.5 \times e^{-\ln(G_0)}) \text{ could be rewritten as:}$$

$$\text{IR}_{\text{HOMA}} = (I_0 \times G_0) / 22.5 \text{ (mathematically: } e^{-\ln x} = 1/x).$$

It is appropriate to apply this index in large epidemiological studies where only fasting insulin and glucose values are available (STUMVOLL and GERICH 2001).

### QUICKI

The quantitative insulin sensitivity check index (QUICKI) can be determined from fasting plasma glucose (mg/dl) and insulin ( $\mu$ IU/ml) concentrations (KATZ et al. 2000).

$$\text{QUICKI} = 1 / (\log I_0 + \log G_0)$$

The reported values of QUICKI were  $0.382 \pm 0.007$  for non-obese,  $0.331 \pm 0.010$  for obese and  $0.304 \pm 0.007$  for diabetic individuals. The authors correlated QUICKI and insulin sensitivity index obtained from HEC with the correlation coefficient 0.78;  $p < 2 \times 10^{-12}$ . They, however, did not exclude the possibility of a slightly less significant correlation to be found in future studies.

### McAuley index

The authors (MCAULEY et al. 2001) proposed a formula for predicting insulin resistance in normoglycemic individuals. Regression analysis was used to estimate the cut-off points and the importance of various data for insulin resistance (fasting concentrations of insulin, triglycerides, aspartate aminotransferase, BMI, waist circumference). A bootstrap procedure was used to find an index most strongly correlating with insulin sensitivity index, corrected for fat-free mass obtained by hyperinsulinemic euglycemic clamp (Mffm/I). An insulin sensitivity obtained from HEC of  $\leq 6.3$  (expressed as glucose disposal rate in milligrams per kilogram per minute divided by average plasma insulin concentration in mIU/l) was seen as a cut-off point for individuals with insulin resistance. The combination of fasting insulin (mIU/l) and triglycerides (TAG, mmol/l) showed the best prediction of insulin resistance as follows:

$$\text{Mffm/I} = e^{(2.63 - 0.28 \ln(I_0) - 0.31 \ln(\text{TAG}_0))}$$

### Matsuda index

The index of whole-body insulin sensitivity, proposed by MATSUDA and DEFONZO (1999) combines both hepatic and peripheral tissue insulin sensitivity. This index is calculated from plasma glucose (mg/dl) and insulin (mIU/l) concentrations in fasting state and during OGTT. The correlation coefficients between  $ISI_{\text{Matsuda}}$  and HEC were 0.73 ( $p < 0.0001$ ) in subjects with normal glucose tolerance, 0.66 ( $p < 0.0001$ ) in subjects with impaired glucose tolerance (MATSUDA and DEFONZO 1999), and 0.60 ( $p < 0.0005$ ) in non-diabetic subjects generally (STUMVOLL et al. 2000). However, in subjects with diabetes mellitus Type 2 the correlation proved to be weaker 0.54 ( $p < 0.0001$ )

$$ISI_{(\text{Matsuda})} = \frac{10000}{\sqrt{G_0 \times I_0 \times G_{\text{mean}} \times I_{\text{mean}}}}, \text{ where}$$

- $I_0$  – fasting plasma insulin concentration (mIU/l),
- $G_0$  – fasting plasma glucose concentration (mg/dl),
- $G_{\text{mean}}$  – mean plasma glucose concentration during OGTT (mg/dl),
- $I_{\text{mean}}$  – mean plasma insulin concentration during OGTT (mIU/l),
- 10000 – simplifying constant to get numbers from 0 to 12
- $\sqrt{\phantom{x}}$  – correction of the nonlinear values distribution.

### Belfiore index

The condition for calculation of the Belfiore formulas is the definition of the normal value for basal glucose and insulin concentrations and for mean normal value for glucose and insulin areas during OGTT (BELFIORE et al. 1998). The main point of the Belfiore formulas is the comparison of insulin and glucose values measured (fasting, 0-1-2h areas or 0-2h areas) with the defined normal reference values.

$$ISI_{\text{Belfiore}} = \frac{2}{\frac{G_S}{G_N} \times \frac{I_S}{I_N} + 1}, \text{ where}$$

- $G_S, G_N$  – plasma glucose concentrations expressed as fasting values or as areas obtained dur-

ing a standard OGTT at 0 and 2 h (0-2h areas are equal to  $G_{S,N} = G_0 + G_{120}$ ) or at 0, 1 and 2 h (0-1-2h areas are equal to  $G_{S,N}$

$$= \frac{1}{2} G_0 + G_{60} + G_{120});$$

- $I_S, I_N$  – plasma insulin concentrations expressed as fasting values or as areas obtained during a standard OGTT at 0 and 2 h (0-2h areas are equal to  $I_{S,N} = I_0 + I_{120}$ ) or at 0, 1 and 2 h (0-1-2h areas are equal to  $I_{S,N} = I_0 + I_{60} + I_{120}$ ).

The subscripts S and N refer to “subjects” and “normal reference values”, respectively. Insulin sensitivity calculated using these formulas can achieve only values between 0 and 2. In subjects with normal insulin sensitivity is it around 1; in overweight subjects, in subjects with impaired glucose tolerance and with diabetes Type 2 this value is below 1. Correlation coefficients between  $ISI_{\text{Belfiore}}$  and HEC were in the original study reported to be 0.93 – 0.99;  $p < 0.05$  – 0.01 (BELFIORE et al. 1998). Other authors (MATSUDA and DEFONZO 1999) found lower correlation coefficients of these formulas with HEC: 0.65;  $p < 0.01$  in subjects with normal glucose tolerance, 0.54;  $p < 0.01$  in subjects with impaired glucose tolerance, and 0.48;  $p < 0.01$  in subjects with diabetes Type 2.

### Cederholm index

The insulin sensitivity index proposed by CEDERHOLM and WIBELL (1990) represents mainly peripheral insulin sensitivity and muscular glucose uptake, due to the dominant role of peripheral tissues in glucose disposal after an oral glucose load (KATZ et al. 1983).

$$ISI_{\text{Cederholm}} = \frac{75000 + (G_0 - G_{120}) \times 1.15 \times 180 \times 0.19 \times m}{120 \times G_{\text{mean}} \times \log(I_{\text{mean}})},$$

where

- 75000 – oral glucose load in an OGTT in mg,
- $G_0$  – fasting plasma glucose concentration (mmol/l),
- $G_{120}$  – plasma glucose concentration in the 120<sup>th</sup> min of OGTT (mmol/l),
- 1.15 – factor transforming whole venous blood glucose to plasma values (not necessary, if glucose concentration is estimated in plasma),

- 180 – conversion factor to transform plasma glucose concentration from mmol/l into mg/l,  
 0.19 – glucose space in liter per kg of body weight,  
 m – body weight (kg),  
 120 – duration of OGTT (min),  
 $I_{\text{mean}}$  – mean plasma insulin concentration during OGTT (mIU/l),  
 $G_{\text{mean}}$  – mean plasma glucose concentration during OGTT (mmol/l).

Values found in normal non-obese individuals were reported to be about  $79 \pm 14 \text{ mg.l}^2.\text{mmol}^{-1}.\text{mIU}^{-1}.\text{min}^{-1}$ , lower in obese individuals, in subjects with impaired glucose tolerance and in patients with diabetes Type 2 (CEDERHOLM and WIBELL 1990). MATSUDA and DEFRONZO (1999) determined correlation coefficients of this index with HEC: 0.52 ( $p < 0.05$ ) in subjects with normal glucose tolerance, 0.48 ( $p < 0.05$ ) in subjects with impaired glucose tolerance, and 0.40 ( $p < 0.05$ ) in subjects with diabetes Type 2.

Other authors (STUMVOLL et al. 2000) determined correlation coefficients of this index with HEC and found it to be 0.60 ( $p < 0.0005$ ) in non-diabetic subjects.

#### Gutt index (GUTT et al. 2000)

This index ( $ISI_{0,120}$ ) was adapted from the insulin sensitivity index proposed by CEDERHOLM and WIBELL (1990).  $ISI_{0,120}$  is expressed in  $\text{mg.l}^2.\text{mmol}^{-1}.\text{mIU}^{-1}.\text{min}^{-1}$ . Its calculation uses, in contrast to ISI Cederholm, only the fasting (0 min) and 120 min concentrations of glucose and insulin in OGTT. Insulin concentration is expressed in mIU/l and glucose concentration in mg/dl in the nominator and in mmol/l in the denominator.

$$ISI_{0,120} = \frac{75000 + (G_0 - G_{120}) \times 0.19 \times m}{120 \times G_{\text{mean}} \times \log(I_{\text{mean}})}$$

The index correlated well with the insulin sensitivity index obtained from HEC (0.63;  $p < 0.001$ ). This index exhibited a good ability to predict diabetes mellitus Type 2 in a large prospective study (HANLEY et al. 2003).

#### Avignon index

The authors (AVIGNON et al. 1999) proposed 3 insulin sensitivity indices: Sib (derived from fasting plasma insulin and glucose concentrations), Si2h (derived from plasma insulin and glucose concentrations in the 120<sup>th</sup> min of OGTT) and SiM (derived by averaging Sib and Si2h after balancing Sib by a coefficient of 0.137 to give the same weight to both indices).

$$Sib = 10^8 / (I_0 \times G_0 \times VD),$$

$$Si2h = 10^8 / (I_{120} \times G_{120} \times VD),$$

$$SiM = [(0.137 \times Sib) + Si2h] / 2, \text{ where}$$

I and G represent the plasma concentrations of insulin (mIU/l) and glucose (mmol/l) respectively, VD is the glucose distribution volume calculated using a monocompartmental model:  $VD = 150 \text{ ml/kg}$  of body weight (COBELLI et al. 1987).

The SiM index correlated well with insulin sensitivity obtained during insulin-modified frequently sampled intravenous glucose tolerance test (FSIVGTT; BERGMAN et al. 1987) in individuals with normal glucose tolerance (0.89;  $p \leq 0.0001$ ), with impaired glucose tolerance (0.96;  $p \leq 0.0001$ ), and in patients with diabetes mellitus Type 2 (0.83;  $p \leq 0.05$ ) (AVIGNON et al. 1999). It is important to note that other indices mentioned in this paper were correlated with the clamp method (DEFRONZO et al. 1979), seen as the “gold standard” in estimating insulin sensitivity. The correlation coefficients of FSIVGTT and the euglycemic clamp were reported to be 0.84 ( $p < 0.002$ ) (BEARD et al. 1986), 0.89 ( $p < 0.001$ ) (BERGMAN et al. 1987), and 0.62 ( $p < 0.05$ ) (SAAD et al. 1994), diminishing the weight of the Avignon indices to the level of the other indices discussed.

#### Stumvoll index

STUMVOLL et al. (2000, 2001) proposed a series of indices (approximately 10) calculated from plasma glucose (mmol/l) and insulin (pmol/l) concentrations during OGTT. The equations were generated using the multiple linear regression analysis and adapted to the availabilities of sampling times during OGTT and of demographic parameters (BMI, age). Their cor-

relation coefficients with HEC were in the range between 0.62 and 0.79 ( $p < 0.001$ ).

An example equation could be the index of insulin sensitivity calculated from data obtained in 0, 60 and 120 min of OGTT either with or without demographic data:

$$ISI_{\text{Stumvoll}} = 0.222 - 0.00333 \times \text{BMI} - 0.0000779 \times I_{120} - 0.000422 \times \text{Age} \quad (r=0.79; p<0.001),$$

$$ISI_{\text{Stumvoll}} = 0.156 - 0.0000459 \times I_{120} - 0.000321 \times I_0 - 0.00541 \times G_{120} \quad (r=0.69; p<0.001).$$

### Discussion

Estimation of impaired insulin sensitivity should be of high importance mainly in individuals with risk factors present. Approximately 20% of the whole non-diabetic population has impaired insulin sensitivity (MATSUDA and DEFONZO 1999). This number is higher in obese non-diabetic subjects (FERRANNINI et al. 1997).

Only a part of the amount on insulin sensitivity indices proposed in the literature was mentioned in this paper. An insulin resistance index ( $FIRI = I_0 \times G_0 / 25$ ) (DUNCAN et al. 1995) is similar to the  $IR_{\text{HOMA}}$  index.  $G_0/I_0$  ratio was also used as insulin sensitivity index (LEGRO et al 1998). However, the use of this index is not recommended because of confusing results (MATSUDA and DEFONZO 1999). The choice of an index depends on sampling times during OGTT. The optimal sampling constellation based on the data reviewed

seems to be 0, 30, 60 and 120 min of the OGTT in those equations where mean values are required.

All results of the aforementioned equations should be handled from a critical point of view because none of the OGTT indices reveal the exact same information as the insulin sensitivity obtained during a hyperinsulinemic euglycemic clamp. The reviewed indices of insulin sensitivity have to be seen as a pre-disease predictive parameter for the development of diabetes mellitus based on insulin resistance. Their use is not appropriate in the diabetic population. In diabetic individuals the correlation coefficients of the indices and HEC were much lower than in the non-diabetic population (MATSUDA and DEFONZO 1999, AVIGNON et al. 1999). The importance of the indices lies in their use in large epidemiological studies for assessment of relations between selected variables (CERVENAKOVA et al. 2002). For fasting values, insulin resistance is defined by WHO as the highest quartile of the  $IR_{\text{HOMA}}$  index in non-diabetic subjects (ALBERTI and ZIMMET 1998). Insulin resistance is also defined as the lowest decile of insulin sensitivity in the lean subgroup of non-diabetic population (FERRANNINI et al. 1997). In clinical practice, however, their application is limited due to the lack of exact reference values.

The major role of the insulin sensitivity indices seems to be a) to predict the development of diabetes mellitus Type 2 in healthy population and in individuals with impaired glucose metabolism and b) to assess the degree of insulin sensitivity in non-diabetic population with risk factors present.

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Corresponding author: Žofia Rádiková MD  
Institute of Experimental Endocrinology  
Slovak Academy of Sciences  
Vlarska 3  
833 06 Bratislava, Slovakia  
e-mail: Zofia.Cervenakova@savba.sk  
phone: 00421-2-5477 4942  
fax: 00421-2-5477 4247