

COMPARISON OF DIFFERENT ASSESSMENT MODELS OF INSULIN RESISTANCE IN ROMANIAN OBESE PATIENTS

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Abstract

Insulin resistance is either an associated condition or is considered to be a predictor or pathogenic factor in various human pathological states such as type 2 diabetes mellitus, glucose intolerance, obesity, polycystic ovary syndrome, essential hypertension, metabolic syndrome and, more recently, atherosclerosis. The standard method for the evaluation of insulin resistance is the euglycemic hyperinsulinemic clamp technique. Direct determination of insulin sensitivity with the hyperinsulinemic-euglycemic clamp technique is laborious and impractical in large human studies. Since it is important to have accessible methods to estimate insulin secretion and sensitivity in the human body, mathematical models for the evaluation of insulin resistance have been developed.

The main purpose of our study was to assess the relevance of different mathematical models for the evaluation of insulin resistance in the biochemical evaluation of a group of Romanian obese patients. Our results show that the homeostasis model assessment parameters (HOMA) and the Quicki test (Quantitative insulin sensitivity check index) vary significantly in correlation with both weight and glucose level in a group of Romanian subjects.

Rezumat

Rezistența la insulină reprezintă, fie un factor predictiv sau patogenic, fie un fenomen patologic asociat în numeroase afecțiuni complexe cum ar fi diabetul zaharat de tip 2, intoleranța la glucoză, obezitatea, sindromul ovarian polichistic, hipertensiunea esențială, sindromul metabolic și conform cercetărilor recente, ateroscleroza. Metoda standard de evaluare a rezistenței la insulină este tehnica *euglycemic hyperinsulinemic clamp*. Această metodă este laborioasă și nu poate fi aplicată în studii clinice extinse. Deoarece este important să existe metode accesibile de evaluare a rezistenței la insulină, au fost create modele matematice pentru cuantificarea acestui fenomen.

Principalul scop al prezentului studiu a fost acela de a testa relevanța unor modele matematice de evaluare a rezistenței la insulină în contextul evaluării biochimice a unui grup de pacienți obezi din România.

Rezultatele evidențiază faptul că parametrii modelului de homeostazie glucidică și testul Quicki variază semnificativ în raport cu greutatea corporală și respectiv cu glicemia pacienților selectați.

Keywords: insulin resistance, obesity; Quicki test; HOMA

Introduction

The control of blood glucose homeostasis is mainly due to two closely related physiological mechanisms: the capacity of the pancreas to secrete insulin and the biological action of this hormone on insulin-sensitive tissues, especially liver, muscle and adipose tissue [1]. It is well known that in various human pathological states such as type 2 diabetes mellitus, glucose intolerance, obesity, polycystic ovary syndrome, essential hypertension, metabolic syndrome and, more recently, atherosclerosis, insulin resistance (IR) is either an associated condition or is considered to be a predictor or pathogenic factor [2, 3, 4, 5].

Insulin resistance (IR) is the condition in which normal amounts of insulin are inadequate to produce a normal physiologic response in the main target tissues of the pancreas hormone (fat, muscle, liver) [6].

Insulin resistance reduces the effects of insulin and results in elevated hydrolysis of triglycerides stored in the fat cells, leading to an increase of the free fatty acids' level in plasma. Insulin resistance in muscle cells reduces the glucose uptake, whereas in liver cells results in impaired glycogen synthesis and a failure to suppress glucose production. All these phenomena lead to reduced muscle glucose uptake and increased liver glucose production, thus contributing to the elevation of the blood glucose level, and accelerating the glucose toxicity associated with the insulin resistance [7].

The concept that insulin resistance may be one of the main causes of type 2 diabetes mellitus was first defined by Wilhelm Falta and confirmed by Harold Percival Himsworth in 1936 [8,9].

The concept of insulin resistance is relatively easy to understand, but determining precisely who is insulin resistant is more complicated. The relationship between glucose and insulin is quite complex and involves the interaction of many metabolic and regulatory factors. Normal insulin sensitivity varies widely and is influenced by age, ethnicity, and obesity; so, not all people with impaired insulin sensitivity are necessarily suffering from a disorder, pregnancy being an example of this situation [10].

The general signs of insulin resistance are: fatigue (physical and/or mental), intestinal bloating caused by carbohydrates in the diet, weight gain, fat storage in and around abdominal organs in both males and females, difficulty losing weight, impaired lipid levels, increased blood pressure, sometimes depression, etc.

Therefore, it is important to have methods to estimate insulin secretion and sensitivity in the human body [1].

Literature data specifies that the most efficient and scientifically correct methods for the evaluation of insulin resistance are “clamp” techniques. These procedures require i.v. access, multiple venipunctures, and take a long time, thus being relatively impractical for office assessment. The euglycemic hyperinsulinemic clamp technique is the reference method, the “gold standard” for quantifying insulin sensitivity or resistance *in vivo* because it directly measures the effects of insulin on glucose use under steady state conditions [1]. Besides the euglycemic hyperinsulinemic clamp technique, other clamp techniques have been developed: frequently sampled IV glucose tolerance test (FSIVGTT), insulin tolerance test (ITT), insulin sensitivity test (IST), and continuous infusion of glucose with model assessment (CIGMA). There are also some models available for the evaluation of insulin resistance depending on glucose and insulin levels in oral glucose tolerance tests: Insulin Sensitivity Index (ISI), Matsuda test, Caderholm test, Gut test, etc.

Unfortunately, most of these methods share the disadvantages of the euglycemic hyperinsulinemic clamp, requiring i.v. access, multiple blood sampling, glucose/insulin infusion for several hours, being also difficult to use for the patients and for the specialists [11].

Largely because of the fact that the standard methods for assessing beta-cell function and insulin sensitivity, the hyperglycemic and euglycemic glucose clamps, are complex and costly to perform, several studies have been conducted to determine simpler and more applicable assessments [10].

So the mathematical models for the evaluation of insulin resistance depending on fasting levels of glucose and insulin began to be used.

The most popular test of this kind is the Homeostatic model assessment (HOMA) of β -cell function and insulin resistance and it was first described in 1985 [12]. This test represents a method for assessing β -cell function and IR from basal glucose and insulin or C peptide concentrations. The model has been widely used since it was first published. [13, 14, 15].

Recent data mentioned some other models for the evaluation of insulin resistance. Quantitative Insulin Sensitivity Check Index (QUICKI) can be evaluated depending on fasting levels of glucose and insulin. Many investigators believe that QUICKI is superior to HOMA as a way of determining insulin sensitivity [16, 17, 18].

The main purpose of our study was to assess the relevance of different mathematical models for the evaluation of insulin resistance in the biochemical evaluation of a group of Romanian obese patients. We also evaluated the association of parameters for insulin resistance/sensitivity with markers of the beta cell function for the study group.

Materials and methods

Subjects and study design

We included in our study 63 patients, 37 women (58.73%) and 26 men (41.26%), 40 to 60 years old, hospitalized at the N. Paulescu National Institute of Diabetes and Metabolic Diseases. Any past or present insulin treatment, along with any hematological or kidney diseases were an exclusion criterion. The protocol was approved by the local ethics committee and the informed consent of the patients was obtained.

Biochemical evaluation

For the studied patients we assessed, on *à jeun* blood samples, the following parameters: fasting plasma glucose (FPG), fasting plasma insulin, plasma lipids and lipoproteins (total cholesterol - TC, triglycerides -TG, low density lipoproteins - LDL, high density lipoproteins - HDL), plasma insulin level.

Fasting plasma glucose and plasma lipids (TC, LDL, and HDL) were determined using automatic devices and commercial kits (Merck and Biorad). Insulin was evaluated using an ELISA kit (Diagnostic Systems Laboratories) on a ChemWell 1000 device. Using the values of fasting plasma glucose and insulin, several insulin sensitivity indexes have been evaluated (Quicki, HOMA-IR, HOMA-B).

QUICKI was calculated according to the report by Katz et al. with the formula

$$\text{QUICKI} = \frac{1}{\log(\text{fasting insulin } (\mu\text{UI/mL})) + \log(\text{fasting glucose } (\text{mg/dL}))}$$

The equations used for the homeostatic model assessment are:

$$\text{HOMA-IR} = \frac{\text{fasting glucose (mmoles/L)} \times \text{fasting insulin } (\mu\text{UI/mL})}{22.5}$$

for insulin resistance and

$$\text{HOMA-B} = \frac{20 \times \text{fasting insulin } (\mu\text{UI/mL})}{\text{fasting glucose (mmoles/L)} - 3.5}$$

for β -cell function, respectively.

1/HOMA-IR and $\log(\text{HOMA-IR})$ were also calculated [12, 13, 14].

Statistical analysis

Results are reported as means $\pm$ standard deviation (SD). Student *t* test was appropriately used for group comparisons. Correlations were assessed by a non-parametric test (Spearman). P values <0.05 were considered statistically significant.

Results and discussion

The patients were divided into three groups, according to their body mass index (BMI):

- control group (n=11), BMI<25 kg/m²
- overweight group (n=25), 25 kg/m²<BMI<30 kg/m²
- obese group (n=27), BMI>30 kg/m²

The BMI was calculated according to the formula:

BMI = (Weight/height²) and expressed as Kg/m².

Table I shows the clinical characteristics of all three studied groups.

Table I
The biochemical parameters for the overweight and obese patients compared to the control group

Evaluated parameters	Control group	Overweight group	p value overweight vs. control	Obese group	p value obese vs. control
BMI (kg/m ²)	21.46±2.02	27.28±1.61	<0.0001	35.04±4.74	<0.0001
Fasting plasma glucose (mg/dL)	85.8±7.25	128.2±74.17	0.009	163.24±73.80	<0.0001
Total cholesterol (mg/dL)	176.60±34.46	201.05±38.48	0.04	216.8±37.11	0.003
LDL cholesterol (mg/dL)	100.18±39.10	119.48±37.18	NS*	133.51±30.72	0.01
HDL cholesterol (mg/dL)	60.20±13.17	48.47±11.34	0.014	48,80±15.52	0.04
Triglycerides (mg/dL)	81.10±55.67	86.75±52.61	NS*	173.36±129.21	0.002

*NS – not significant

Our results show that the weight increase is associated with a disturbance of the glycemic and lipid homeostasis. The fasting plasma glucose, total cholesterol and the lipoprotein levels increased from the control group to the other two studied groups. The LDL and TG increased significantly at the obese patients compared to controls, but not significantly at overweight patients compared to controls. All the other parameters increased significantly both in the overweight and the obese groups compared to the lean group.

Many investigators have studied simple surrogate indices of insulin resistance in comparison with the index assessed by euglycemic-hyperinsulinemic clamp. It has been established that homeostasis model assessment of insulin resistance HOMA-IR is a useful surrogate index of insulin resistance in diabetic and nondiabetic subjects and that its logarithmic transformation or its reciprocal value might make it more accurate [17, 18].

The HOMA model allows the evaluation of an insulin resistance index (HOMA-IR) and also of an index for the β -cell function (HOMA-B). These two parameters estimate the deficiency of the pancreatic β -cells based on a mathematical model that takes into account the interrelation (by negative feed-back) between glucose and insulin under normal metabolic control. This interrelation involves both the secretion of the pancreatic hormone and the hypoglycemic insulin action on target tissues.

QUICKI is also defined as a result of the *in vivo* interaction between glucose and insulin in fasting conditions and, according to some investigators, reflects even better than HOMA, the variations of the insulin sensitivity of target tissues.

The literature data does not define reference values for HOMA and for QUICKI parameters.

For the studied patients we evaluated HOMA-IR and HOMA-B, the reciprocal value of HOMA-IR, QUICKI (table II).

Table II
Parameters for the evaluation of beta cell function and insulin resistance

Evaluated parameters	Control group	Overweight group	p value overweight vs. control	Obese group	p value obese vs. control
Insulin (μ UI/mL)	5.73 $\pm$ 1.23	5.93 $\pm$ 1.65	NS*	8.17 $\pm$ 4.51	0.009
Glucose/Insulin	15.69 $\pm$ 3.91	22.04 $\pm$ 11.06	0.019	23.38 $\pm$ 15.38	0.013
HOMA-IR	1.28 $\pm$ 0.27	1.96 $\pm$ 1.37	0.01	3.57 $\pm$ 2.92	0.0003
1/HOMA-IR	0.86 $\pm$ 0.17	0.68 $\pm$ 0.28	0.022	0.50 $\pm$ 0.34	0.0001
Log(HOMA-IR)	0.103 $\pm$ 0.07	0.24 $\pm$ 0.22	0.01	0.46 $\pm$ 0.33	<0.0001
HOMA-B	99.31 $\pm$ 38.63	67.72 $\pm$ 46.44	0.03	47.30 $\pm$ 29.58	0.001
QUICKI	2.44 $\pm$ 0.53	2.02 $\pm$ 0.71	0.04	1.62 $\pm$ 0.84	0.0009

*NS – not significant

For the selected group, the insulin level increased non-significantly at overweight patients and very significantly to obese patients compared to controls. So, only the fasting level of insulin does not indicate the degree of insulin resistance. Also, the glucose/insulin ratio is significantly different in the overweight and obese groups compared to controls, but does not differ between the two pathological groups.

The American Diabetes Association defines pre-diabetes by levels of fasting plasma glucose (FPG) between 100 and 125 mg/dL. Analyzing the dynamics of insulin resistance parameters in the group of selected patients in correlation with the FPG level, we obtained the values presented in table III.

Table III
Parameters for the evaluation of beta cell function
and insulin resistance in correlation with the fasting plasma glucose level

Evaluated parameters	Control group	Overweight group		Obese group	
	FPG<100mg/dL	FPG<100mg/dL	FPG>125mg/dL	FPG<100mg/dL	FPG>125mg/dL
Insulin (μ UI/mL)	5.73 $\pm$ 1.23	5.68 $\pm$ 0.81	6.72 $\pm$ 2.79	5.53 $\pm$ 1.30	10.22 $\pm$ 5.29
Glucose/Insulin	15.69 $\pm$ 3.91	15.51 $\pm$ 2.49	35.09 $\pm$ 14.63	17.34 $\pm$ 3.65	29.50 $\pm$ 19.34
HOMA-IR	1.28 $\pm$ 0.27	1.22 $\pm$ 0.21	3.55 $\pm$ 1.63	1.26 $\pm$ 0.35	5.58 $\pm$ 2.78
1/HOMA-IR	0.86 $\pm$ 0.17	0.85 $\pm$ 0.17	0.35 $\pm$ 0.18	0.84 $\pm$ 0.20	0.22 $\pm$ 0.10
Log(HOMA-IR)	0.103 $\pm$ 0.07	0.11 $\pm$ 0.05	0.51 $\pm$ 0.22	0.12 $\pm$ 0.09	0.70 $\pm$ 0.21
HOMA-B	99.31 $\pm$ 38.63	96.64 $\pm$ 36.39	19.99 $\pm$ 13.17	70.51 $\pm$ 19.01	25.04 $\pm$ 17.92
QUICKI	2.44 $\pm$ 0.53	2.42 $\pm$ 0.57	1.24 $\pm$ 0.36	2.41 $\pm$ 0.65	0.99 $\pm$ 0.20

The analysis of the data depending both on the BMI and the fasting plasma glucose, shows that all of the parameters defined for the evaluation of insulin resistance and beta cell function increase significantly in the groups with FPG>125mg/dL.

The control group and the overweight and obese groups with FPG<100mg/dL had similar values of the evaluated parameters. The groups with FPG>125mg/dL, either overweight or obese showed significant increases of the parameters for the evaluation of insulin resistance or beta cell function compared to the control group (fig 1, fig2).

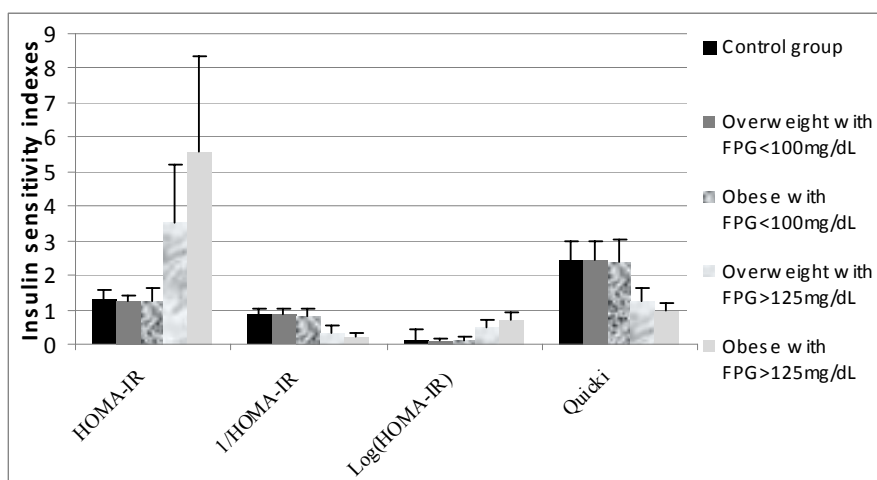
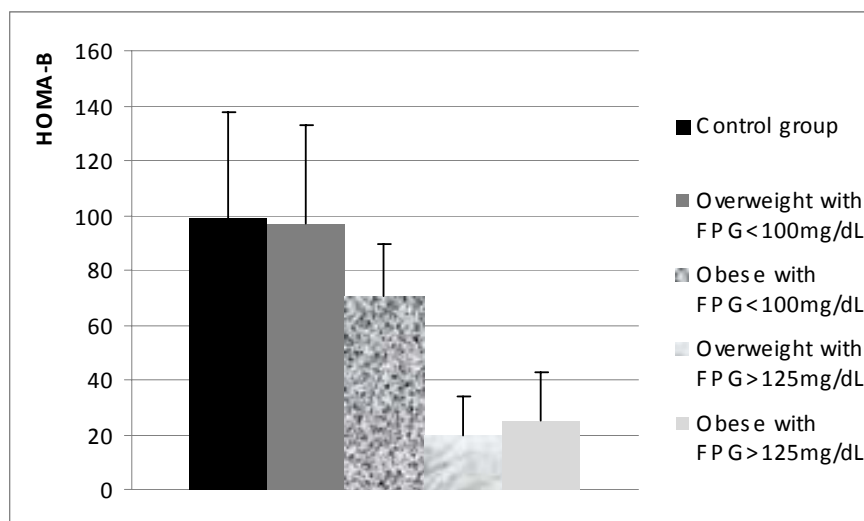


Figure 1

Distribution of the insulin sensitivity indexes in the groups and subgroups of patients included in the study

**Figure 2**

HOMA-B (as insulin sensitivity index) values in the groups and subgroups of patients included in the study

Conclusions

Since insulin resistance is frequently associated as predictor or pathogenic factor in different pathological conditions (type 2 diabetes mellitus, obesity, glucose intolerance, essential hypertension, polycystic ovary syndrome, it is important to have simple, accessible tools for the evaluation of insulin sensitivity of target tissues to the insulin action in humans. The euglycemic hyperinsulinemic clamp technique remains the reference method for quantifying the sensitivity to insulin action but it cannot be applied on a large scale or in the context of routine investigations. For this reason, alternative methods have been developed, including the HOMA model and the Quicki test.

Our results show that the above mentioned parameters vary significantly in correlation with both weight and glucose level in a group of Romanian subjects.

The parameters for the evaluation of insulin resistance and beta cell function might be used in clinical studies in correlation with the level of fasting plasma glucose and not simply as indicators of the degree of insulin resistance in overweight and obese patients.

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