INSULIN RESISTANCE MARKERS IN TYPE 1 DIABETES MELLITUS

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Abstract

Insulin resistance (IR) is a fundamental disorder of type 2 Diabetes Mellitus (DM), but it is also involved in the etiopathogenesis of type 1 DM, with important implications in the onset and progression of micro- and macrovascular complications in type 1 DM. Overweight plays the main role in the increased incidence of both types of DM, exacerbating IR. The epidemic increase of overweight and obesity makes it difficult to diagnose the exact phenotype of DM, as IR and autoimmunity often coexist. Many studies showed an increase in incidence of micro- and macrovascular complications in patients with type 1 DM with IR, compared to patients with type 1 DM without IR. The gold standard of IR evaluation is represented by the method of euglycemic-hyperinsulinemic clamp, applied on a reduced scale in research. Thus, it is necessary to identify early IR markers (clinical or biological markers), less laboured ones, that could be used on a large scale in current medical practice, for the IR determination in type 1 DM. Clinicians and health experts should prevent/reduce the epidemic of overweight and obesity in young people, thus decreasing IR, and implicitly the chronic complications of DM.

key words: insulin resistance, type 1 Diabetes Mellitus, chronic complications, IR markers

Introduction

Insulin resistance (IR) is defined as „a condition where a certain insulin concentration triggers a biological response lower than the normal one” [1,2].

Although IR is considered a fundamental disorder of type 2 Diabetes Mellitus (DM), its intervention in type 1 DM is more and more brought under discussion in the last period [1,3,4]. IR having also important implications in the onset and progression of micro- and macrovascular complications in type 1 DM [4,5].
The gold standard of IR evaluation is represented by the method of euglycemic-hyperinsulinemic clamp [1,6], applied on a reduced scale and usually for research purposes [1,6]. Therefore, it is necessary to identify less laborious markers for the assessment of IR in type 1 DM patients, markers which could be used on a large scale in current medical practice.

The suspicion of IR intervention in type 1 DM has started from the high variation of exogene insulin doses required to obtain the same degree of glycemic control in type 1 DM (from a low dose to doses over 2 UI/kg, and even higher) [6].

The “accelerator hypothesis” as a unifier mechanism of type 1 and type 2 DM

The “accelerator hypothesis” was proposed by Wilkin (2001) as a unifier mechanism of type 1 and type 2 DM, representing two phenotype expressions of the same disease, the difference between them being made by the β-cells loss rate and by the presence of accelerators. Type 1 and 2 DM would actually be the same IR disease that emerges on a different genetic background [6-8].

According to Wilkin, the three accelerators are: a high intrinsic rate of β-cells apoptosis, genetically determined [6,7]; overweight and IR, which increase the rate of β-cells apoptosis, thus accelerating the onset of type 1 and 2 DM [6,7]; and β-cells autoimmunity (in a small number of cases) – in the patients with accelerated apoptosis and IR, which increases the β-cells loss rate, diverting the pathological process towards type 1 DM [6,7].

But none of the accelerators leads to DM in the lack of overweight, which plays the main role in the increase of both types of DM incidence, by the exacerbation of IR [6]. Glucotoxicity directly accelerates apoptosis and, by inducing the β-cells imunogenes, it subsequently accelerates it towards a genetic subset prone to autoimmunity [6]. Body weight control, and implicitly control of IR, may represent the way of reducing the increase rate of DM incidence, in general [6].

The epidemic increase of overweight and obesity makes it difficult to diagnose the type of DM, as IR and autoimmunity often coexist [9-11]. Some of the patients with type 1 DM have the disease onset at an adult age, with a quite slow evolution and without a tendency towards ketosis, or without any insulin requirement for years. On the other hand, type 2 DM can be also diagnosed in teenagers and young people, sometimes with ketoacidosis, the insulin dependence onset occurring after some time [7]. Thus, the notions of type 1 and 2 DM may be considered as artificial, as insulin dependence for the glycemic control is the final stage that all types of DM reach, sooner or later [7], according to the concept of “β-cells loss time”. The rate of β-cells loss determines the age of DM onset: never, in adulthood or childhood. Only time makes the difference between the childhood onset from the adulthood onset forms of DM [7].

Arguments supporting the “accelerator hypothesis” in type 1 DM

1. The incidence of type 1 DM increases at the same time with the increase of obesity frequency in children (IR indicator). Thus, in the last 2 decades, the prevalence of obesity in children doubled in some regions of the world [6,7,12]. The prevalence of the metabolic syndrome (MS) in children and teenagers with severe obesity in the South of China reached 22.1% [13]. MS, as a clinical effect of IR, is found in patients with type 1 DM in various percentages; thus, in patients from the Pittsburg Epidemiology of Diabetes Complications Study it varies from 8% (MS defined according to the criteria of International Diabetes Federation - IDF) [14] to 21% (MS defined according to
World Health Organization - WHO) [14]. In another study, the prevalence of MS in caucasians patients with type 1 DM ≥ 18 years was 31.9% [4]. In two groups of Romanian patients with type 1 DM, MS was diagnosed according to American Heart Association / The National Heart, Lung, and Blood Institute (AHA/NHLBI 2009) consensus criteria in a percent of 28.6% [15], respectively 25% [16].

2. *Children with type 1 DM and a higher degree of obesity develop an earlier disease* [6,7].

3. *Children in the first stage of the disease have a higher weight in the first 2-3 years of life, than the ones that remain healthy (the cause precedes the effect)* [6,7].

4. *In monozygotic twins presenting a risk for type 1 DM risk, the ones developing type 1 DM have a higher IR and a smaller β-cells storage than the ones that do not develop DM* [6,7].

5. Out of the children presenting a genetic risk for type 1 DM, the ones with *the highest basal IR degree* are usually the most prone to develop type 1 DM [6,7].

### Other arguments for IR intervention in type 1 DM

1. *The frequent onset of the disease during puberty*, a period associated with a higher IR. On the background of preexistent and enough advanced β-cell dysfunction, this IR induces the progression from a stage of glucose tolerance disturbance to a clear clinical manifest type 1 DM [6,17].

2. *IR acts in prediabetes*, but there are great differences of prediabetes evolution towards type 1 DM. Probably the IR degree (increased during puberty or in obesity) is the one inclining the balance on one side or the other [6].

3. *IR also exists after the clinical onset of type 1 DM*, an argument for this being the onset of the temporary remission („honey moon”) in type 1 DM, manifested by an important decrease of the exogenous insulin requirements. Some authors explain remission by the improvement of the endogenous insulin secretion as a consequence of the diminished pancreatic islands inflammatory reaction. Others state that there is a temporary improvement of the IR status present at diagnosis, namely the increase of tissular sensitivity towards insulin [6,17]. The latter hypothesis seems more plausible since the C-peptide (having an equimolar secretion with insulin which estimates the residual β-cell function) measurement did not indicate any increase of its concentration during the oral glucose tolerance test (OGTT) or during other tests for insulin secretion stimulation, although the patients were in remission. Instead, the direct measurement of IR, through the euglycemic-hyperinsulinemic clamp method, confirmed that insulin sensitivity increases in those in remission, correlated with the necessary insulin dose and with HbA1c [6]. There are studies which showed that the „honey moon” end is accompanied by an increase in IR [6].

4. **Reduction of the insulin like growth factor-1 (IGF-1) concentration**. IGF-1 is an important modulator of insulin sensitivity during puberty; it is synthesized in the liver, having insulin-like effects on glucose uptake in peripheral tissues and on hepatic glucose production. In type 1 DM, due to portal hypoinsulinemia, IGF-1 level is reduced, with a compensatory increase in the growth hormone (GH), which antagonizes the insulin effects. The high seric levels of GH determine the synthesis of higher quantity of proteins binding IGF-1, thus decreasing the free seric IGF-1 [6].

5. *Hyperglycemia and/or hypoinsulinemia increase IR*. It was shown that insulin action is lower after 24 hours of hyperglycemia, in comparison to 24 hours of euglycemia. This fact suggests that hyperglycemia induces IR. It was suggested that intensive insulinc treatment
determines a good glycemic control by reducing the IR [6].

6. Metformin also acts in type 1 DM. Thus, placebo controlled studies highlighted a reduction with 25.8% [18], respectively 18% [19] of the insulin requirements in patients with type 1 DM that received metformin associated to insulin treatment [20]. Metformin also proved to be efficient in treating obese teenagers with MS (administered after the age of 10 years), combined with a change in their lifestyle [13].

7. Finally, many studies showed an increase in incidence of micro- and macrovascular complications in patients with type 1 DM with IR, compared to patients with type 1 DM without IR [4,21-24].

Identifying the IR markers in type 1 DM may have serious therapeutical implications, especially in preventing complications of type 1 DM.

Clinical risk factors for IR

1. Abdominal circumference (AC): AC ≥ 80 cm in European women and ≥ 94 cm in European men (according to the IDF 2005 criteria for defining MS) is associated with IR and high risk for cardiovascular diseases (CVD) [25]. AC may represent a simple and practical alternative (that does not involve high costs) for estimating IR when no laboratory data is available. Thus, 60% of the variation of glucose disposal rate (GDR) is explained only by AC [26].


According to BMI values, subjects are included in the following categories: 18.5 – 24.9 kg/m² = normal; < 18.5 = underweight; 24.9 – 29.9 = overweight; 30 – 34.9 = 1st degree obesity; 35 – 39.9 = 2nd degree obesity; ≥ 40 = 3rd degree obesity [27].

3. Waist to Hip ratio (WHR): Abdominal circumference / Hip circumference (HC), with normal values < 0.85 in women and < 0.9 in men [27,28]. A high WHR is an IR marker and it is associated with high risk for chronic complications in type 1 DM. Thus, WHR positively correlates with TG, systolic blood pressure (sBP), diastolic blood pressure (dBP) and it negatively correlates with HDL-cholesterol [29].

4. Waist to Height ratio also identifies patients with metabolic risk. Normal value of AC/H is < 0.5 [27,30].

Methods for IR estimation in type 1 DM subjects

Since the classic methods frequently used for the estimation of IR, including insulinema, HOmeostasis Model Assessment - Insulin Resistance (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), and the Matsuda - DeFronzo insulin sensitivity index (ISI-M) have insulinema in their calculation formula, they cannot be used in patients treated with insulin, including patients with type 1 DM. For these patients were developed other insulin-sensitivity (IS) scores, validated by the euglycemic-hyperglycemic clamp method.

1. HOMA represents a mathematic model that assesses the IS degree (HOMA%S) and the level of beta-cellular function (HOMA %B), through the simultaneous measurement of fasting glycemia and fasting insulinema. It is used on a large scale in non-insulin treated patients with type 2 DM, simple to apply, reproducible and well-correlated (r = 0.88) with the estimations that use the gold standard of euglycemic-hyperglycemic clamp method.

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The formula involves the introduction of data regarding glycemia (mmol/l or mg/dl), insulinemia (pmol/l or μU/ml) or C-peptide (nmol/l or ng/ml), automatically calculating %B, %S and IR. In insulin treated patients, fasting C-peptide is used instead of insulinemia [31].

2. **HOMA – IR modified with fasting C-peptide** [32] may be applied in assessing IR and beta cell function in DM patients using exogenous insulin. A Chinese study showed that HOMA and modified HOMA were similar in normal subjects and in those with DM [32].

IR models were determined by multiple linear regression, using \((C\text{-peptide} \times \text{glycemia})\) as independent variable and **HOMA-IR** as dependent variable [32]. Models of the beta cell function were determined using \((C\text{-peptide/fasting glycemia} - 3.5)\) as independent variable and **HOMA islet** as dependent variable [32]. The fasting C-peptide modified HOMA formulas are:

\[
\text{HOMA-IR (C-peptide)} = 1.5 + \left[ \text{fasting glycemia (mg/dl)} \times \text{fasting C-peptide (ng/ml)} \right] / 2800
\]

\[
\text{HOMA-islet (C-peptide - Normal)} = 0.27 \times \text{fasting C-peptide} / \left( \text{fasting glycemia} - 3.5 \right) + 50
\]

\[
\text{HOMA-islet (C-peptide - DM)} = 0.27 \times \text{fasting C-peptide} / \left( \text{fasting glycemia} - 3.5 \right) [32].
\]

It was shown that HOMA-IR (C-peptide) significantly correlates with HOMA-IR \((r = 0.689)\) while Homa-islet (C-peptide) significantly correlates with Homa-islet \((r = 0.788); p = 0.000 [32].

3. **Fasting C-peptide**

Normal values of C-peptide are the following:

- children between 5 and 15 years old – \(\text{fasting} = 0.4 – 2.2 \text{ ng/ml (mean 1 ng/ml)}\);
- adults - \(\text{fasting} = 0.4 – 2.1 \text{ ng/ml (mean 1.1 ng/ml)}\);
- 2 hours after meal = 1.2-3.4 ng/ml (mean 1.8 ng/ml);

- after 2 hours post load during the OGTT = 2-4.5 ng/ml (mean 3 ng/ml);
- in urine: 20 nmol/24 hours (type 1 DM < 5 nmol/24 hours) [33].

Conversion factors for C-peptide: 1 nmol/l=1 pmol/ml =3.9 ng/ml=3.9 μg/l [33].

In type 1 DM patients with a low but detectable C-peptide, the risk for renal and nervous complications is lower than in patients with absent C-peptide [33]. The combined treatment for 3 months with insulin and injectable C-peptide (600 nmol/24 h) improved renal function in patients with type 1 DM and incipient nephropathy, reducing the albumin urinary excretion (AUE), and also ameliorated autonomous and peripheral neuropathy in patients with type 1 DM [33,34], enhancing the cold-sensitivity threshold [33].

Fasting C-peptide strongly correlated with known IR markers (HOMA-IR, QUICKI, insulinemia) in patients without DM. Thus, the subjects in the quartile with the highest C-peptide (≥ 0.984 nmol/l) presented a 60% higher risk for cardiovascular mortality, and a 72% higher risk for all cause of mortality, compared to the subjects in the quartile with the lowest C-peptide (≤ 0.418 nmol/l) [35].

C-peptide is also a possible early biomarker for CVD in obese subjects, C-peptide exhibiting 4 significant correlations with other components of the MS (HDL-cholesterol, leptin, AC and uric acid), compared to insulinemia, which presented only 2 significant correlations (dBP and leptin) [36].

4. **Another index used for the IR screening in patients with type 2 DM is the following:**

\[
20/[\text{fasting C-peptide (nmol/L)} \times \text{fasting glycemia (mmol/L})].
\]

This index may also be used in type 1 DM, having the C-peptide and not insulinemia in its calculation formula, and is more efficient than HOMA-IR, QUICKI and ISI in estimating IR. Thus, in the patients with DM
and mild IR (mild IR was defined in patients with the glucose infusion rate (GIR) during the euglycemic-hyperinsulinemic clamp between 5 and 10 mg·kg$^{-1}$·min$^{-1}$), the index 20/(fasting C-peptide × fasting glycemia) strongly correlated with GIR (r = 0.90, P < 0.0005), unlike HOMA-IR, ISI and QUICKI, which did not correlate with the GIR [37]. The mean value of the index 20/(fasting C-peptide × fasting glycemia) in patients with type 2 DM in this study was of 5 [37].

5. The C-peptide index (CPI) is calculated with the following formula: fasting C-peptide (nmol/L)/ fasting glycemia (mmol/L) × 100 [37,38].

6. Another index of insulin sensitivity assessment in non-diabetic subjects is the Clamp-like index (CLIX), which uses the level of glycemia and C-peptide during OGTT and the level of seric creatinine. CLIX is calculated with the following formula: seric creatinine (mg/mL) (×0.85 in men)/(mean of the area under the curve glycemia (mg/dl) × mean of the area under the curve C-peptide (ng/mL)) × 6,600 [37,39]. It strongly correlates with GIR and it even detects slight changes of the insulin sensitivity, thus being as accurate as the euglycemic-hyperinsulinemic clamp [37,39].

7. The index [fasting C-peptide (nmol/L) + postprandial C-peptide (nmol/L)] × [fasting glycemia (mmol/L) + postprandial glycemia (mmol/L)] assesses the IR at glucose load, significantly being correlated with GIR even in patients with DM and mild IR [37].

8. The Triglycerides (TG) (mmol/l) / HDL cholesterol (mmol/l) ratio (Reaven score). Values ≥ 3 represent an IR marker and an independent predictive factor for cardiovascular events and mortality [40,41].

9. Increased seric TG level represents an independent predictive factor for the development and progression of microvascular complications (renal and ocular) in patients with type 1 DM, only in those with normoalbuminuria [42].

10. Total Cholesterol / HDL cholesterol ratio ≥ 5 is associated with a high risk for CVD [43].

11. Estimated Glucose Disposal Rate (eGDR) - IR was assessed by eGDR with a validated formula in studies on the euglycemic-hyperinsulinemic clamp in 24 non-hispanic white adults with type 1 DM for a long period of time, using WHR, hypertensive status - antecedents of high blood pressure (HBP) (yes = 1, no = 0) and glycemic control (value of glycated hemoglobin HbA1c %) according to the formula eGDR (mg x kg$^{-1}$ x min$^{-1}$) = 24.31 – (12.22 x WHR) – (3.29 x HBP) – (0.57 x HbA$_{1c}$) [29]. A low value of eGDR indicates a high IR [4, 29,44].

In this study [29], eGDR was strongly correlated with IR measured by clamp (r = 0.79). The strongest inverse correlation with eGDR were HbA1c, WHR, AC and TG. There were also strong inverse correlation between eGDR and BMI and the daily insulin dose (U · kg$^{-1}$ · day$^{-1}$) [29].

When HC is not available to calculate WHR, there may be used an equation only with AC, having similar results (eGDR calculated with AC was strongly correlated with eGDR calculated with WHR, r = 0.87): eGDR (mg x kg$^{-1}$ x min$^{-1}$) = 21.158 – [0.090 × AC (cm)] - [3.407 × HBP] – [0.551 × HbA$_{1c}$] [29].

It was shown that patients with MS presented lower values of eGDR in comparison to those without MS (6.19 ± 1.5 mg x kg$^{-1}$ x min$^{-1}$ vs. 9.93 ± 1.6 mg x kg$^{-1}$ x min$^{-1}$) [4]. eGDR level < 8.77 mg x kg$^{-1}$ x min$^{-1}$ presents 100% accuracy and 85.2% specificity for the MS diagnosis in type 1 DM [4].

Patients with DM complications have eGDR values < 8.16 mg x kg$^{-1}$ x min$^{-1}$ [4]. The
eGDR levels are significantly lower in the patients with DM complications: diabetic retinopathy (5.97 ± 1.2 mg x kg⁻¹ x min⁻¹), diabetic neuropathy (5.06 ± 0.4 mg x kg⁻¹ x min⁻¹) or diabetic nephropathy (5.79 ± 1.5 mg x kg⁻¹ x min⁻¹), compared to those without any complications (9.38 ± 2.0 mg x kg⁻¹ x min⁻¹; 9.26 ± 2.0 mg x kg⁻¹ x min⁻¹ and respectively 9.19 ± 2.2 mg x kg⁻¹ x min⁻¹) [4], being a predictive factor for retinopathy, nephropathy [5, 14, 21, 45, 46], neuropathy [5, 47] and CVD in type 1 DM [14, 21, 45].

eGDR has an inverse correlation with age: eGDR (mg/kg/min) = 12.51 − [0.26 × age (years old)] [14, 44]; eGDR adjusted to age was significantly correlated: negatively with the percentage of the adipose tissue, TG, urinary albumin/creatinine ratio (ACR), acanthosis nigricans, parental obesity and parental IR (at least 1 obese parent/ 1 parent with IR) [29, 44].

eGDR was positively correlated with sex hormone–binding globulin (SHBG); a low level of SHBG is associated with a higher IR (eGDR increases by 0.96 mg·kg⁻¹·min⁻¹ in an increase of SHBG by 10 nmol/l) [44]. eGDR does not differ according to sex [44].

eGDR has an inverse correlation with the DM duration: eGDR (mg/kg /min) = 10.15 − [0.19 × DM duration (years)] (insignificant correlation after the age adjustment) [14, 44].

eGDR significantly correlated with ethnicity (race) in type 1 DM; eGDR was significantly lower (8.42 ± 2.74) in the non-white patients (non-Hispanic black, others/mixed and Hispanic) compared with non-Hispanic whites (10.34 ± 2.16) [44]; this IR variation was observed in young persons with a short DM duration and normal adiposity, suggesting that ethnic/ racial differences have an early presence in the disease [44]; the black race had a significantly lower eGDR (5.66 ± 2.34) than the Hispanics (6.70 ± 2.29) and the white race (7.20 ± 2.03) [45].

In another study, the eGDR was assessed in type 1 DM patients with intensive insulin therapy, aged between 5 and 16 years old, comparing overweight or obese children to normal weight children [48]. eGDR did not significantly differ in normal weight, overweight or obese children, but obese children > 11 years old had the lowest value of eGDR. The insulin dosis (UI/m²/day) was higher in overweight and obese children [48].

Sleep restriction (a night with 4 hours of sleep vs. 7 hours of sleep) decreases GDR during the clamp, thus reflecting the decrease of insulin peripheral sensitivity; also, sleep restriction decreases GIR by approximately 21% [49].

12. There is an estimated Insulin Sensitivity score (IS) that explains 74% of the GDR variation, validated in a subgroup of 85 patients with DM from the SEARCH Study [26] and 22 control subjects who were subjected to the euglycemic-hyperinsulinemic clamp method. The score included usual clinical data, such as: AC, TG and HbA1c level. Thus, this score can easily estimate the IR in young people with DM in epidemiological studies [26].

The best proposed formula for the estimated IS score in young people with DM is the following: log(IS) = 4.64725 - 0.02032 (AC, cm) - 0.09779 (HbA1c, %) − 0.00235 (TG, mg/dl) [26]. The most practical formula for estimating the IS score is: log(IS) = 3.7339- 0.02155 (AC, cm) [26].

The estimated IS score had a good correlation with GDR, both in young people with DM (also in young people with type 1 and 2 DM), as well as in the control young people, without DM. The IS score should be used with caution in children during puberty [26].

The relation between the estimated IS score and fasting C-peptide in all the participants in the SEARCH study was a line of two spleen regression slopes with a loop in an IS score of 7.7 and a C-peptide level of 0.14 nmol/l [26].
SEARCH, an observational, longitudinal study, also analyzed in what measure the etiological type of DM (autoimmunity and IR) are associated with the albuminuria level in the young people with newly diagnosed type 1 and type 2 DM [9]. The young people with DM were distributed according to diabetes autoantibody (DAA) status and IR presence. Patients with a positive DAA were those having positive titres for glutamatic acid decarboxylase antibodies (GADA) or insulinoma-associated 2 antibodies (IA-2A) [9]; IR was defined as the estimated IS score values (arbitrary cutoff) < 25 percentile for the general young population of USA (< 8.15). The patients were divided into 4 etiological types of DM: DAA+/insulin sensitive (IS); DAA+/insulin resistant (IR); DAA-/IR; DAA-/IS [9]. IR was significantly associated with the degree of albuminuria, the DAA+/IR group having the highest ACR [9].

There are studies that demonstrated a significant correlation between age, sex, DM duration, level of seric lipids (except for HDL-cholesterol), daily insulin dose, leukocytes and ferritin with the IR progression in type 1 DM [50].

Conclusions

All these evidences that support the role of IR in the onset and progression of micro- and macrovascular complications in type 1 DM should motivate clinicians and healthcare experts to prevent/reduce the epidemic of overweight and obesity in young people, which plays the main role in the onset of IR. Identification of markers for the assessment of IR in patients with type 1 DM, which could be used on a large scale in current medical practice, may help to reduce the large costs associated with the cronic complications of DM.

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