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Acta Medica Marisiensis 2013;59(6):279-284 DOI: 10.2478/amma-2013-0064

RESEARCH ARTICLE

Surrogate Measures of Insulin Resistance in Middle-aged Non-diabetic Subjects

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Objective: Insulin resistance has been shown to be a risk factor for type 2 diabetes and cardiovascular disease. The assessment of insulin sensitivity in the clinical practice, however, faces several difficulties. The study proposes to analyze surrogate measures of insulin resistance based on fasting insulin levels in central Romania, and check whether the diagnosis of the metabolic syndrome is an adequate strategy to identify middle-aged persons with reduced insulin sensitivity.

Methods: Anthropometric measurements, metabolic profile, and surrogates measures of insulin sensitivity (GIR, HOMA, QUICKI, FIRI, Belfiore, Bennett, Raynaud, McAuley index) based on fasting insulin levels were assessed in 233 non-diabetic middle aged subjects.

Results: Cutoff values, determined as the lowest quartile of insulin sensitivity for fasting insulin, HOMA, IRI (1/QUICKI), FIRI and Belfiore's, Bennett's, Raynaud's and McAuley's insulin sensitivity indices were 10.49 mU/L, 2.1, 3.01, 2.32, and 0.03, 1.34, 3.81, 6.29, 5.82. Components of the metabolic syndrome showed moderate but significant correlations with the surrogate measures of insulin resistance ($r = 0.22–0.56$, $p < 0.05$). HOMA-IR and McAuley indices were the best predictors of clustered cardiometabolic risk factors (AUC - 0.83, 0.81 and 0.82). The metabolic syndrome diagnosis performed well in identifying patients with reduced insulin sensitivity (McAuley 2: sensitivity – 0.78, specificity – 0.84).

Conclusion: Fasting insulin derived insulin sensitivity indices may help the recognittion of insulin resistant states predicting cardiometabolic disorders. Actively looking for insulin resistance by these simple indices, or by diagnosing the metabolic syndrome, those at increased risk can be recognized.

Keywords: insulin resistance, metabolic syndrome

Received: 4 October 2013

Introduction

Type 2 diabetes and cardiovascular diseases show an increasing morbidity and mortality in populations characterized by a Western lifestyle. Insulin resistance, which frequently accompanies obesity, has been shown to be a risk factor for type 2 diabetes, as well as for cardiovascular diseases even in the absence of diabetes, so it is currently considered an independent predictor for age related disorders [1,2]. The basis of efficient prevention is risk assessment in the young and middle-aged; one strategy could be the early detection of reduced insulin sensitivity [3]. Measurements of insulin sensitivity, however, are currently done only for research purposes, and there are no generally accepted criteria to identify those with insulin resistance. Indirect and surrogate estimates have been proposed, but the lack of standardized insulin assays, and ethnic differences make the results of published studies difficult to compare; in addition, the accessibility of insulin assays remains limited in our region. This is why alternative strategies are needed for identifying persons who present decreased insulin sensitivity and, thus, might be at increased cardiometabolic risk. The present study proposes to assess the cutoff values of surrogate measures of insulin resistance based on various formulae using fasting insulin levels, in a population from central Romania, and checked whether the diagnostic criteria of the metabolic syndrome elaborated by the International Diabetes Federation in 2004 including the mandatory presence of abdominal obesity was an adequate strategy to identify middle-aged persons with reduced insulin sensitivity in the condition of low accesibility of insulin assays, so far characteristic for the region.

Material and methods

One-hundred twenty-four healthy middle-aged subjects and 109 persons with the metabolic syndrome have been recruited from the County Emergency Clinical Hospital and Empatia Medical Center between 2003-2006. Anthropometric measurements were taken, and biochemical assays have been done using the Hitachi© 717 Roche analyzer from the Central Laboratory of the County Hospital. Fasting insulinemia was determined by ELISA using DakoCytomation Insulin kits. Surrogate measure of insulin sensitivity (ISI – insulin sensitivity index) and resistance (IR – insulin resistance index, or 1/ISI) based on fasting insulin levels have been calculated in MS Excel spreadsheets using the following formulae:

- FI – fasting insulin (mU/L);
- Raynuad's ISI: 40/FI (mU/L); [4]
- GIR – glucose-insulin ratio: FI/FG (FI – mU/L; FG – mg/dL);

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- IR, HOMA 2 calculator version 2.2; (http://www.dtu.ox.ac.uk/homacalculator/index.php);
- HOMA-IR: (FI × FG)/22.5 (FI – mU/l; FG – mmol/L); [5]
- QUICKI: 1/[log FI + log FG] (FI – mU/L; FG – mg/dL); [6]
- FIRI – fasting insulin resistance index: (FI × FG)/25; [7]
- Bennett's ISI: 1/(log FG × log FI) (FI – mU/l; FG – mmol/L); [8]
- Belfiore's basal ISI: 2/[(FI × FG) + 1] (FI – mU/l; FG – mmol/L); [9]
- McAuley ISI-1: exp [2.63 – 0.28 lnFI – 0.31 lnTG) (FI – mU/L; TG – mmol/L);
- McAuley ISI-2: exp [3.29 – 0.25 lnFI – 0.2 ln BMI – 0.28 lnTG) (FI – mU/L; TG – mmol/L) [10].

The presence of the metabolic syndrome was assessed based on the criteria recommended in 2004 by the IDF [11]. The protocol has been approved by the local Ethics Committee, and written informed consent was obtained from all subjects who agreed to participate in the study. Descriptive statistics have been calculated using Statistica version 6 (StatSoft Inc., 2001). Pearson correlation coefficients as well as the diagnostic value of the procedures (sensitivity, specificity, PPV - positive predictive value, NPV - negative predictive value, LR - likelihood ratio) have been calculated using GraphPad InStat version 3.00 for Windows 95. A ROC (receiver operating characteristics) analysis using the web-based calculator developed by Eng [12] was conducted to evaluate the ability of the metabolic syndrome to correctly identify those with insulin resistance; the overall diagnostic accuracy was quantified using AUC (area under ROC curve). In all cases, a p value < 0.05 was considered statistically significant.

Results

Demographic data as well as the metabolic characterization of the healthy non-diabetic subjects used to identify cutoff points of insulin resistance indices based on fasting insulin values, as well as of the patients with the metabolic syndrome used to test the capacity of the diagnostic criteria proposed by the International Diabetes Federation in 2004 to identify reduced insulin sensitivity states are presented in Table I.

Table I. Demographic data and metabolic characterization

	Non-diabetic healthy subjects	Metabolic syndrome patients
Number	124	109
Age in years (mean±SD, median)	52.1 ± 16.11 (50)	57.75 ± 10.43 (58)
Male/Female (%)	58/66 (46.8/53.2)	52/57 (47.7/52.3)
Urban/Rural domicile (%)	85/39 (68.5 /31.4)	57/52 (52.3/47.7)
Fasting glucose (mg/dL)	95.09 ± 12.58 (94.35)	123.03 ± 42.81 (110)
Fasting insulin (mU/L)	9.21 ± 7.04 (7.23)	13.30 ± 7.81 (11.36)
BMI (kg/m^2)	25.59 ± 5.33 (24.64)	32.15 ± 6.1 (32)
Waist circumference (cm)		
Male	98.55 ± 11.92 (97.5)	113.13 ± 13.35 (111)
Female	86.93 ± 12.64 (86)	107.42 ± 12.78 (107)
Systolic blood pressure (mmHg)	128.44 ± 20.37 (125)	156.06 ± 20.28 (155)
Diastolic blood pressure (mmHg)	79.12 ± 11.86 (80)	90.58 ± 11.51 (90)
Triglyceride (mg/dL)	124.34 ± 84.77 (109.5)	215.79 ± 152 (171)
HDL-cholesterol (mg/dL)		
Male	50.21 ± 12.3 (53.15)	47.52 ± 18 (46.08)
Female	53.67 ± 11.6 (53.5)	50.33 ± 21.91 (50)
Uric acid (mg/dL)	5.03 ± 2.03 (5.15)	7.12 ± 1.88 (7.1)
ALAT (U/L)	18.57 ± 7.18 (16.3)	30.12 ± 23.29 (26)

Insulin sensitivity and resistance indices based on fasting blood insulin levels according to quartiles in the healthy middle-aged group in order to assess the cutoff points as the lowest quartile of insulin sensitivity indices to estimate insulin resitance are shown in Table II.

Correlations between insulin sensitivity/resistance indices and components of the metabolic syndrome found in the healthy subjects are represented in Table III.

Correlations of insulin sensitivity indices with the components of the metabolic syndrome, except for blood pressure, have been moderate but significant; the highest correlations have been seen between insulin sensitivity and abdominal circumference and tryglyceride levels.

ROC curves showing the ability of the metabolic syndrome to identify insulin resistance as assessed by indices derived from fasting insulin levels are represented in Figure 1. The diagnostic power of the metabolic syndrome

Table II. Surrogate measures of insulin sensitivity in non-diabetic healthy subjects

ISI /IR surrogate index	25th percentile	50th percentile	75th precentile	Mean	SD	Min–Max
Fasting glucose (mmol/L)	4.77	5.24	5.27	5.28	0.68	3.72–7.1
Fasting insulin (mU/L)	4.6	7.23	10.49	9.21	7.04	1.6–34.48
Raynaud's ISI	3.81	5.53	8.69	6.63	4.26	1.07
GIR	8.99	13.48	20.66	15.25	8.99	2.64–51.62
FIRI	0.88	1.75	2.32	2.02	1.52	0.29–9.08
IR, HOMA Calculator v. 2.2	0.6	0.95	1.4	1.2	0.9	0.4–4.7
HOMA-IR	0.65	1.69	2.1	1.71	1.42	0.07–9.16
IRI (1/QUICKI)	2.59	2.83	3.01	2.84	0.31	2.12–3.61
Bennett's ISI	1.34	1.61	2.22	1.86	0.93	0.78–7.4
Belfiore's ISI	0.03	0.05	0.87	0.06	0.04	0.008–0.24
McAuley-1 ISI	6.29	8.19	8.98	7.8	2.09	3.37 –14.19
McAuley-2 ISI	5.92	7.44	8.06	7.02	1.72	3.32–10.69

Table III. Correlation of fasting insulin-derived surrogate measures of insulin sensitivity and the components of the metabolic syndrome

	FI	Raynaud's ISI	GIR	FIRI	IR – HOMA Calculator v. 2.2	HOMA-IR	IRI (1/QUICKI)	Bennett's ISI	Belfiore's ISI	McAuley's ISI-1	McAuley's ISI-2
Waist circumference	0.29 (0.07–0.048)	-0.29 (-0.48 – -0.07), 0.01	-0.28 (-0.47–0.05), 0.015	0.35 (0.14–0.53), 0.002	0.38 (0.17–0.56) 0.0007	0.33 (0.116–0.52), 0.003	0.35 (0.14–0.53), 0.0019	-0.262 (-0.46 – -0.04), 0.02	-0.49 (-0.64 – -0.3), <0.0001	-0.38 (-0.55 – -0.17), 0.0005	-0.38 (-0.56 – -0.16), 0.001
Fasting glucose	0.38 (0.18–0.55), 0.0004	-0.38 (-0.55 – -0.18), 0.0004	-0.25 (-0.45 – -0.04), 0.021	0.55 (0.38–0.69), <0.001	0.44 (0.25–0.6), <0.0001	0.37 (0.27–0.54), 0.001	0.56 (0.39–0.69), <0.0001	-0.22 (-0.41 – -0.004), 0.046	-0.49 (-0.64 – -0.3), <0.0001	-0.38 (-0.54 – -0.17), 0.0005	-0.38 (-0.56 – -0.16), 0.001
Systolic blood pressure	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	-0.23 (-0.44 – -0.001), 0.04	-0.22 (-0.43 – -0.02), 0.07
Diastolic blood pressure	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	-0.27 (-0.47 – -0.05), 0.02	-0.26 (-0.46 – -0.01), 0.03
Triglyceride	0.25 (0.03–0.44), 0.022	-0.25 (-0.44 – -0.036), 0.02	-0.25 (-0.44–0.03), 0.02	0.42 (0.22–0.58), 0.0001	0.42 (0.22–0.58), <0.0001	0.39 (0.55–0.88), 0.0003	0.37 (0.16–0.54), 0.0007	-0.209 (-0.407 – -0.008), 0.05	-0.25 (-0.41 – -0.03), 0.02	-0.73 (-0.82 – -0.6), <0.001	-0.71 (-0.81 – -0.57), <0.001
HDL-cholesterol	-0.36 (-0.57 – -0.09), 0.009	0.36 (0.09–0.57), 0.008	0.33 (0.06–0.55), 0.02	-0.27 (-0.47 – - 0.03), 0.02	-0.32 (-0.47 – -0.07), 0.01	-0.31 (-0.47 – -0.06), 0.01	-0.32 (-0.54 – -0.06), 0.001	0.032 (0.54–0.005), 0.02	0.37 (0.11–0.58), 0.006	0.36 (0.1–0.54), 0.005	0.39 (0.11–0.61), 0.007

Data with 95%CI in paranthesis and the p value

Table IV. Diagnostic power of the metabolic syndrome diagnosed according to the IDF criteria in identifying impaired insulin sensitivity assesed by fasting insulin-derived surrogate measures

	AUC	SE	Sensibility (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	LR	p
Fasting insulin	0.72	0.03	0.82 (0.7–0.9)	0.58 (0.48–0.62)	0.52 (0.41–0.62)	0.85 (0.75–0.93)	1.94	<0.0001
1/GIR	0.64	0.04	0.44 (0.34–0.55)	0.81 (0.71–0.89)	0.73 (0.6–0.84)	0.56 (0.46–0.65)	2.35	0.0006
HOMA Calculator v. 2.2	0.74	0.03	0.62 (0.51–0.72)	0.88 (0.78–0.94)	0.85 (0.75–0.93)	0.66 (0.56–0.75)	4.94	<0.0001
HOMA-IR	0.83	0.03	0.73 (0.63–0.82)	0.81 (0.7–0.89)	0.82 (0.72–0.9)	0.72 (0.61–0.81)	3.8	<0.0001
IRI (1/QUICKI)	0.77	0.03	0.64 (0.53–0.74)	0.83 (0.73–0.9)	0.8 (0.7–0.89)	0.67 (0.57–0.76)	3.76	<0.0001
FIRI	0.77	0.03	0.7 (0.6–0.79)	0.69 (0.58–0.78)	0.69 (0.59–0.78)	0.8 (0.7–0.88)	4.87	<0.0001
1/Raynaud's ISI	0.72	0.03	0.6 (0.51–0.68)	0.72 (0.53–0.86)	0.9 (0.83–0.96)	0.29 (0.19–0.4)	2.13	0.0015
1/ Bennett's ISI	0.78	0.03	0.8 (0.7–0.88)	0.69 (0.58–0.78)	0.69 (0.59–0.78)	0.8 (0.7–0.88)	2.58	<0.0001
1/ Belfiore's ISI	0.77	0.03	0.82 (0.72–0.9)	0.67 (0.56–0.76)	0.65 (0.55–0.75)	0.83–0.73–0.9)	2.47	<0.0001
1/ McAuley's ISI-1	0.81	0.03	0.78 (0.69–0.86)	0.84 (0.73–0.92)	0.88 (0.79–0.94)	0.73 (0.61–0.82)	4.9	<0.0001
1/McAuley's ISI-2	0.82	0.03	0.82 (0.72–0.89)	0.7 (0.6–0.79)	0.72 (0.61–0.8)	0.81 (0.7–0.89)	2.72	<0.0001

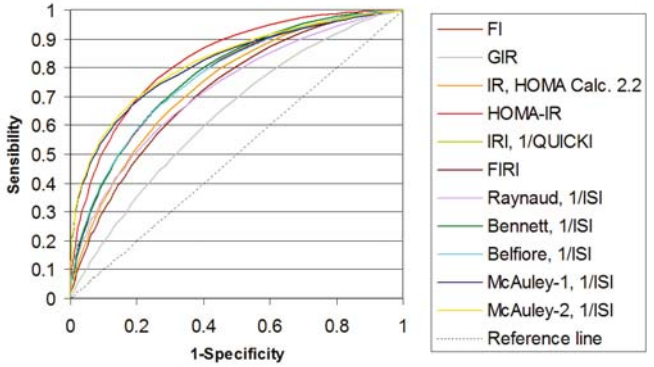

Fig. 1. ROC analysis of the metabolic syndrome diagnosis and insulin resistance indices

in predicting insulin resistance estimated by the proposed formulae based on fasting insulin is shown in Table IV.

Based on the moderate to high AUC data and sensibility and specificity values, the metabolic syndrome diagnosis as recommended by the International Diabetes Federation in 2004 seems an acceptable alternate approach to identify persons with a decreased insulin sensitivity diagnosed by various formulae based on the less accessible fasting insulin assay: positive diagnosis presented the highest likelihood ratio with insulin resistance estimated by the HOMA and McAuley method.

Discussion

There have been many debates in the last two decades regarding the metabolic syndrome. In 2004, in an attempt to unify the diagnosis, the International Diabetes Federation proposed criteria which were modified later and according to which abdominal obesity is no more mandatory but the association of 3 anomalies — abdominal obesity, dysglycemia, atherogenic dyslipidemia and/or high blood pressure — should be sufficient for diagnosis [11,13]. The latest agreement of experts states that such a diagnosis presents no additional clinical utility, and the syndrome should be considered a premorbid condition [14]. It may be disputed whether such a syndrome exists as a distinct entity, but both scientists and clinicians agree, that further studies of the pathogenesis of this cluster of cardiometabolic risk factors are needed. In 1988, Reaven proposed insulin resistance as the common denominator, and though not unanimously accepted, it remains a key, but probably not exclusive, underlying mechanism, supported also by a factor analysis in a Romanian population [15]. Whether the core component of the metabolic syndrome or not, insulin resistance has been identified also as a predictor of cardiometabolic morbidity and mortality [16]. Recently, it has been suggested that diagnosing those with "metabolically unhealthy obesity" based on the presence of insulin resistance could be an efficient strategy for optimal intervention [17].

Unfortunately, assessing reduced insulin sensitivity remains an unsolved problem. The relationship between glucose and insulin is complex, and it is characterized by the interaction of many factors. Normal insulin sensitivity varies widely, influenced by age, ethnicity, obesity, and not all people with insulin resistance actually suffer from it. There are several direct and indirect methods to quantify insulin sensitivity, and the choice of the technique used depends on the information needed, glycaemic status and available resources. The gold standard remains the hyperinsulinaemic-euglycaemic clamp, but it can be performed only in research setting. For epidemiological and clinical studies, simple, indirect methods have been used, which are based on measuring plasma insulin levels during fasting or after glucose stimulus, followed by the calculation of various ratios with different mathematical formulae. In many regions, including our country, however, not even the assessment of fasting insulin is available on large scale. Besides the limited accessibility, standardization of the insulin assays continues to be a main problem [18]. Development of measurements of insulin sensitivity suitable for the clinical practice thus remains necessary, and motivated the curent study. Indirect measures present important limitations, poor reproducibility and reliability. There are neither clear guidelines, nor universally accepted cutoffs available for surrogate markers, they constituting the objective of the presented assesments and calculations in a study group from our population. The European Group for the Study of Insulin Resistance defined insulin resistance as the lowest 10% in a non-obese, non-diabetic, normotensive Caucasian population, while a World Health Organization consensus group concluded that the insulin sensitivity indices of the lowest 25% of a general population could be considered insulin resistant [11,19]; the latter recommendation has been used in this study. There are considerable ethnic differences, and while data for various populations have been published, no publication regarding their systematic assessment and cutoff values for the Romanian population could be found, thus constituting the primary objective of this study. The cutoff values obtained for these indirect measures of insulin sensitivity based on a single fasting insulin sample in our non-diabetic middle-aged subjects are comparable with those described in other populations of Caucasian origin [20], but also in certain Asian countries [21]. Measurements using standardized assays, compared to a reference technique, in a larger sample, and also in different age and body-weight groups would be necessary, but were unavailable, and thus limit the results obtained.

The indices based solely on fasting insulin levels — FI or 1/FI, Raynaud's ISI — present the same limitations. They are relatively cheap and simple methods that do not require complex mathematical calculations. Due to the important daily variance, the average of two samples taken on different days is recommended but this was not possible, and can be considered another important limitation in the interpretation of the obtained results, that should also take into consideration the lack of assay standardization, ethnic differences (the study group comes from a mixed population of Romanians, Hungarians, and Rroma), and glycemic status (assessments not recommended in dysglycemia). Fasting sample-derived indices, using mathematical formulae representing the kinetics of fasting insulin, with or without glucose measurement, are the most commonly used indices due to their simplicity and reduced cost. Reliability varies widely, validation is insufficient, and application may be limited in certain groups with β-cell deficiency (including the elderly); it should also be noted that they reflect more hepatic than peripheral insulin sensitivity. While in the middle-aged non-diabetic group that has been studied they can be reliable, in older and diabetic persons their use may be limited. Indices which incorporate more than one parameter have a higher validity, and are preferable over those utilizing insulin alone: Disse's formula shows

the best performance, but includes non-esterified fatty acid levels, so it was not an option in this study. The two parameters included in the majority of methods are the simultaneously sampled fasting glucose and insulin, and these constituted the assessments used also in this study. Several homeostatic approaches have been developed. Their major weakness consists in considering a linear instead of a parabolic relationship between glucose and insulin. Homeostatic model assessment (HOMA) as well as quantitative insulin sensitivity check index (QUICKI) are widely employed, and have been found to strongly correlate with insulin sensitivity assessed by direct measures. QUICKI is considered by some authors superior to HOMA, and can be used also in hyperglycemic patients. Log/ln transformation of all simple indices results in stronger associations with reference techniques, and therefore should be favored to obtain an improvement in the estimation of insulin sensitivity. Several studies have demonstrated a good correlation between these surrogate measures derived from fasting insulin and insulin sensitivity assessed by the clamp (Pearson's r for FI: –0.61, GIR: 0.02, Raynaud's ISI: 0.61. Belfiore's ISI: 0.67, FIRI: –0.72, HOMA-IR: –0.72, QUICKI: 0.8), with the best correlation in obese patients and policystic ovary syndrome [22]. HOMA-IS, QUICKI, and McAuley's indices correlated well with the basic clamp index, the M-value, even in incipient type 2 diabetes and hypertension (r: 0.342, 0.456, and 0.317, p <0.05), and though HOMA-IR was considered the best fit of clamp-derived insulin sensitivity, QUICKI displayed a better reproducibility [23]. It has been suggested, that to reduce the limitations of these methods, it is sometimes a good approach to use simultaneously multiple simple indices, especially if it is not certain which formula is the most suitable, and it constituted the rationale behind this study. Though QUICKI may be a better choice in dysglycemic patients, HOMA-IR and the McAuley indices appear to perform better in relation with the cardiometabolic risk factors. In the studied healthy middle-aged subjects, correlations of insulin sensitivity indices with the components of the metabolic syndrome, except for blood pressure, have been moderate but significant, and abdominal obesity and atherogenic plasma were the most closely related to insulin resistance. The highest correlations were seen with homeostatic models and formulae comprising multiple and log transformed metabolic parameter data.

Epidemiological data obtained in the recent years concerning the predictive power of reduced insulin sensitivity and/or the metabolic syndrome asociated with it suggest a 2-fold increase in cardiovascular outcomes on the long term [24,25,26,27,28]. The Bruneck study revealed that high HOMA-IR associates with an up to 2.5-fold risk of cardiovascular disorder during a 15-year follow-up [24]. In the Framingham Offspring Study, 2/3 of incident diabetes and 2/5 of cardiovasular events affected those with HOMA-IR in the upper 25% [25]. All these data suggest that surrogate measures of insulin sensitivity (especially HOMA-IR) may be tools for identifying individuals at risk. In the routine clinical setting or the family physician's office, however, due to the limitations of insulin assays, alternatives may be required — their identification was another goal of this study. An approach has been undertaken to assess whether the use of the simple diagnosis of the metabolic syndrome which can be easily done in both the family phsycian's office or clinical setting is or not a suitable strategy to predict impaired insulin sensitivity. Diagnosis was based on the criteria recommended by the International Diabetes Federation in 2005, due to personal experience and previous studies, considered a better approach than the reviewed criteria, because of the fact that in the old definition abdominal obesity generally associated with insulin resistance constitutes a mandatory component. Data obtained supports the initial presumtion that in the absence of better techniques, in order to assess impaired insulin sensitivity and thus individuals at high cardiometabolic risk, diagnosing the metabolic syndrome is an acceptable approach. Using as comparison the reliable MMMAG method, Ascaso et al. found that the most sensitive and specific indirect method to assess insulin sensitivity was the score proposed by McAuley et al. (specificity 0.91, sensitivity 0.75), followed by the presence of the metabolic syndrome (specificity 0.91, sensitivity 0.66) [20]. In the current study, a Youden index of 0.54 was obtained in the case of insulin resistance assessed by HOMA-IR, and an even better diagnostic power of the syndrome was seen when predicting insulin resistance estimated by the McAuley proposed index including triglyceride levels (Youden index: 0.62).

Conclusions

Fasting insulin derived insulin sensitivity indices perform well in insulin resistant states predictive of cardiometabolic disorders, before the development of advanced complications and organ deficiency. Actively looking for insulin resistance by these simple indices, or, if not available, by diagnosing the metabolic syndrome, those at increased risk can be recognized.

Acknowledgements

Herewith, I wish to thank for the grants obtained from the Illyés Foundation necessary for procuring the diagnostic kits, the Empatia Medical Center for assisting the recruitment of study subjects, and the Euromed Medical Center for performing the ELISA.

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