Indirect insulin resistance detection: Current clinical trends and laboratory limitations

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There is a steady increase in the number of overweight and obese people worldwide and increasingly, younger people. Excess adipose tissue impairs the action of insulin, leading to insulin resistance (IR). Tissue IR is a major factor in relation to cardiovascular disease, metabolic syndrome and diabetes. Thus, it is important to recognize at the pre-disease stage with the possibility of therapeutic intervention. IR is assessed using indicators of epidemiological significance, most often calculated from fasting and postprandial glucose and insulin values, so-called indirect indicators of insulin resistance. The most commonly used parameter is the Homeostatic Model Assessment (HOMA). Although the Quantitative Insulin Sensitivity Check Index (QUICKI), Matsuda Index and the Insulin Secretion-Sensitivity Index-2 (ISSI-2) are also used, the values of these indices established for IR vary for different age, sex, populations and ethnic groups. Thus, appropriate reference values of indirect indices should be determined for such groups, and when this is precluded, data from published studies carried out on the most ethnically, socio-economically and age-matched populations should be applied.

Key words: insulin resistance, reference interval, decision limit

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BACKGROUND

Insulin resistance (IR) is a pathological state of disturbance between insulin synthesis and its action in the tissues. In this condition, tissue sensitivity to insulin is reduced, which results in impaired glucose homeostasis[1]. Insulin resistance causes a broad spectrum of clinical symptoms, and participates in many pathological states, such as obesity, glucose intolerance, diabetes mellitus (DM), metabolic syndrome (MS), and cardiovascular diseases (CVD). Many of these disorders are associated with various endocrine, metabolic, and genetic factors, but the influences of individual, socio-economic and dietary factors are also indicated[2]. Current research shows that insulin resistance affects a large middle-aged population of working-age and is particularly associated with overweight and obesity[3]. It is estimated that in highly developed countries as many as 15.5-51.0% of adults are affected by IR (ref.[4-6]). However, recent studies have shown that different metabolic disturbances and insulin resistance may also affect young, apparently healthy people with normal body weight and no overt metabolic disorders, as was confirmed in our own research[7]. Different indirect indices are applied for the purpose of insulin resistance recognition, among them those calculated from fasting glucose and insulin concentration, as well as those derived from its measurement during the oral glucose tolerance test (OGTT) (ref.[8,9]). There are few published studies on decision limits for insulin resistance indices, so this condition is recognized with different frequencies even based on the same indices. The most important factors influencing indices values are age, ethnicity origin and lifestyle, as well as the laboratory methods used for glucose and insulin concentration determination[10]. Because of the lack of official guidelines, efforts towards the determination of reference intervals of insulin resistance indices are still necessary for proper diagnosis[11]. For this reason, it is crucially necessary to define reference values for the indices used in IR diagnosis. This may enable the early detection of metabolic disorders and the introduction of preventive actions, especially for young people.

Establishing reference intervals or decision limits could facilitate the use of indirect insulin resistance indices in routine clinical practice, due to accurate identification of individuals at risk for metabolic diseases and the introduction of personalised therapeutic interventions[12,13]. It is especially important for the practices of primary care physicians and family doctors, with regard to the increased prevalence of insulin resistance in the world population[14]. The aim of this review is to provide information about the most popularly used indirect indices of insulin resistance, insulin sensitivity and beta cell capac-

reliability is limited in subjects with type 1 diabetes mellitus. Quantitative Insulin Sensitivity Check Index is a variation of the HOMA equation, and for its calculation the following formula is used (ref.[26,27]):

$$\text{QUICKI} = \frac{1}{\log \text{ fasting insulin } \left[\frac{\mu U}{mL}\right] + \log \text{ fasting glucose } \left[\frac{mg}{dL}\right]}$$

Matsuda Index

The Matsuda index was developed and published in 1999 by Matsuda et al. to assess total, whole-body insulin sensitivity. This index is calculated from plasma glucose and insulin concentrations obtained from fasting blood samples, and after oral ingestion of 75 g glucose during the OGTT. The index is derived from the following formula[28]:

$$\text{Matsuda Index} = \frac{100\,000}{\sqrt{\text{fasting insulin } \left[\frac{\mu U}{mL}\right] * \text{ fasting glucose } \left[\frac{mg}{dL}\right] * \text{area under the insulin OGTT curve } \left[\frac{\mu U}{mL}\right] * \text{ area under glucose OGTT curve } \left[\frac{mg}{dL}\right]}}$$

Insulin Secretion-Sensitivity Index-2 (ISSI-2)

The Disposition Index was described by Steven E. Kahn[29] in 1993. It evaluates pancreatic beta-cell function after intravenous glucose load and refers to the relationship between insulin sensitivity and insulin secretion, which is a constant value for people with the same level of glucose tolerance. Primarily this index was calculated from insulin sensitivity and insulin secretion values, derived from Frequently Sampled Intravenous Glucose Tolerance Test results. This test, developed by Bergman et al.[30], involves the intravenous injection of glucose and multiple glucose and insulin blood sampling, thus evaluating peripheral and hepatic insulin sensitivity. The Disposition Index can also be calculated from values obtained by the euglycemic clamp. In this model, a peripheral insulin sensitivity value is obtained, therefore, in order to quantify the Disposition Index, hepatic insulin sensitivity should also be estimated.

In many epidemiological and clinical studies, the values obtained from OGTT are used to determine the Disposition Index. The use of indices of beta cells compensation calculated from OGTT results require a hyperbolic relationship between insulin sensitivity and secretion. Therefore, in recent years new methods of evaluating the beta-cell functions were developed, which are analogous to the Disposition Index[31-33]. One of them, published by Retnakaran et al.[34] in 2009, is the Insulin Secretion-Sensitivity Index-2 (ISSI-2). The ISSI-2 is quantified from the area-under-the-insulin-curve (AUCins) and the area-under-the-glucose-curve (AUCgluc) during the extended to minimum 3 blood examination oral glucose tolerance test. The obtained AUCins and AUCgluc ratio is then multiplied by the above mentioned Matsuda index. The Insulin Secretion-Sensitivity Index-2 is calculated from the formula:

$$\text{ISSI-2} = \frac{AUC_{ins\ 0-120}}{AUC_{gluc\ 0-120}} * \text{Mat}$$

However, the final result of ISSI-2 calculations is dependent on the applied glucose and insulin units. To compare values between studies, this should be taken into consideration. Moreover, different methods may be used for AUC calculation[35], so the ISSI-2 values obtained from the same results can differ due to the calculation methods applied.

Choosing a proper index

We presented in this review only those insulin resistance and beta cell efficiency indirect indices which have been well described in the literature and used in clinical practice.

Such a variety of IR indices puts the researcher and the clinician before the choice of the most appropriate IR indices for clinical purpose, when the most reliable metabolic clamp cannot be performed or is not recommended for the patient[28,36]. Borai et al.[37] showed that the methods based on the above-described glucose and insulin measurements both under fasting and glucose loading are the most useful and ultimately the only one to use in routine practice.

However, due to the unavoidable biological and analytical variability of glucose, and in particular insulin determinations[38], indicators based on a repeated glucose and insulin measurements obtained during the OGTT test give a more precise estimation of the severity of insulin resistance and beta cell efficiency than those calculated only in fasting state[39].

Although, in general, during diabetes development, early onset of peripheral insulin resistance before hepatic insulin resistance is indicated[40], our observations suggest that insulin resistance may be reflected in varying degrees in elevated fasting and post-load insulin and glucose concentrations. In our pilot study among young people, we recognized both the liver and peripheral insulin resistance with different frequency[41]. However, euglycemic fasting and impaired glucose tolerance patients were observed at the same time and vice versa. Therefore, in our opinion, the calculation of at least two or more indicators for the same patient also increases the clinical usefulness of the information obtained due to the possibility to deter-

mine the dominant type of insulin resistance, its main mechanism and tissues affected (central, e.g. HOMA 2, QUICKI, peripheral e.g. Matsuda, beta cell performance e.g. ISSI-2) (ref.[42]). However, it should be emphasized that in the development of diabetes, patients progress from hyperinsulinemia to the level of exhaustion of pancreatic beta cells secretory reserves. In these patients, despite insulin resistance, slightly higher or even normal insulin concentrations may be observed, especially in the postprandial state[33]. Therefore, in such causes the indexes calculated in the fasting state will be much more reliable than those calculated after loading, which is a condition requiring the activation of pancreatic secretory reserves.

In monitoring the development of insulin resistance and the effectiveness of therapeutic interventions in order to reduce it, it is important to calculate indicators determined with at least the same analytical methods, and preferably laboratory systems (method and analyzer). This is due to the still insufficient standardization of insulin determinations and the sensitivity of immunochemical methods to internal and external confounders, and consequently to significant interlaboratory differences in the determinations of this parameter.

The mathematical model used to calculate the indicators is also important for the final result. Subsequent modifications and up-grade mathematical formulas, most often based on the use of additional variables or logarithmic' transformation of values. Those mathematical operations allow us to consider factors such as hyperglycemia, hyperinsulinaemia and non-Gaussian distribution of results in the general population in final calculation. The aim of such modifications is to increase the correlation of the obtained results with the gold standard (which is a metabolic clamp) and if such a goal is achieved, it is recommended to use modified indicators such as HOMA2 and QUICKI (ref.[12]).

To the best of our knowledge, physicians in clinical practice and a large number of dietitians, most often use the HOMA index in its original version described by Matthews et al.[23]. This is also confirmed by the fact that HOMA is the most frequently used indicator in epidemiological studies. In the literature, the cut off for IR

Table 1. Procedural steps of reference intervals determination according to CLSI recommendations.

Procedural Steps	Terms and Definitions
1. Establish a list of potential analytical interferences based on the medical and scientific literature. 2. Establish acceptance or exclusion criteria for the potential reference individual as well as an appropriate questionnaire. 3. Execute written consent and completed questionnaire from the research participant. 4. Categorize the potential reference individuals on the basis of the personal information questionnaire findings and the results of their health assessment.	Reference population: population of all reference individuals Reference population consists of reference individuals: people selected for comparison with the use of defined criteria
5. Exclude individuals from the sample group based on the exclusion criteria or results of assessment indicating ill health. 6. Establish an appropriate number of reference individuals, taking into account the desired confidence limits. 7. Properly and consistently prepare each individual for specimen collection for the measurements performed in the accordance with the routine practice. 8. Collect the biological specimens properly and handle them in a manner consistent with the routine procedure for patient specimens. 9. Collect the reference values by analyses of the specimens in accordance with the appropriate methodology, under well-defined measurement conditions and consistent with the routine practice for patient specimens.	Reference sample group: a number of reference individuals statistically adequate to represent the reference population
10. Inspect the obtained reference values and prepare a histogram in order to evaluate the data distribution. 11. Identify potential outliers and data errors.	Reference values: value obtained from a reference sample subject by adequate observation or measurement
12. Analyse the reference values, select an estimation method and estimate reference limits as well as the reference intervals. If necessary, include a partition of subjects into subgroups for separate reference ranges.	Reference distribution: statistical distribution of reference values
13. Document the particular stages and all the performed procedures.	Reference limit: a limit used for descriptive purposes, defined on the basis of reference distribution Reference interval: the range of values within the reference limits, which usually includes 95% of observed values

Table 2. The values of insulin resistance indices designated for different populations using different classification criteria.

Author (year)	Ref.	1. Study population 2. Subject number (n) 3. Sex proportion (W/M) 4. Age (years) mean ± SD (interval)	Method determination of insulin (manufacturer) Method determination of glucose (manufacturer)	Method of decision values determination	Estimated insulin resistance indices	Designated value
1. Graffigna et al., (2005)	53	1. Argentinean-Spanish origin young adults 2. n = 363 3. 95 W and 268 M 4. 37 ± 12 W, 36 ± 11 M years (18-65)	Insulin – chemiluminescent method – CLIA (Immulite) Glucose – enzymatic colorimetric method (no data provided)	Mean ± SD	HOMA1-IR	2.04 ± 1.77 for all 1.87 ± 1.72 for W 2.09 ± 1.79 for M
2. Szurkowska et al., (2005)	54	1. Polish adults with NGT and BMI<25 kg/m^2 2. n = 2838 all population (a reference group – no data provided) 3. No data provided 4. - (35-75) years	Insulin – immunoradiometric method (IRMA, Świerk) Glucose – enzymatic method (no data provided)	Cut-off for insulin resistance identification on: 75th percentile 25th percentile	 HOMA1-IR QUICKI Matsuda index	 > 2.1 < 0.34 < 7.3
3. Tresaco et al., (2005)	55	1. Spanish children with and without obesity 2. n = 140 (72 non-obese, 68 with exogenous obesity) 3. 68 W and 72 M 4. 11.01 ± 2.13 years (7-16)	Insulin – immunometric assay (Immulite) Glucose – enzymatic colorimetric assay (Roche/ Hitachi)	ROC curve for MS identification Cut-off for insulin resistance identification on: 75th percentile	HOMA1-IR HOMA1-IR	2.28 2.83
4. Keskin et al., (2005)	56	1. Turkish children and adolescents with pubertal obesity 2. n = 57 3. 30 W and 27 M 4. 12.04 ± 2.90 years	Insulin – radioimmunoassay method (no data provided) Glucose – oxidase method (no data provided)	ROC curve for insulin resistance identification	HOMA1-IR	3.16
5. Geloneze et al., (2009)	57	1. Nondiabetic Brazilians 2. n = 1203 3. 692 W and 511 M 4. median 41 (Q1-Q3: 32-50) years (18-78)	Insulin – radioimmunoassay method (Linco Research Inc.) Glucose – oxidase method (no data provided)	ROC curve for MS identification Cut-off for insulin resistance identification on: 90th percentile (n=297; selected healthy group)	HOMA1-IR HOMA2 HOMA1-IR HOMA2	2.3 1.4 2.7 1.8

Table 2. *Continued.*

6. d'Annunzio et al., (2009)	58	1. Italian healthy children and adolescents 2. n=142 3. 57 W and 85 M 4. 10.6 ± 3.8 years (2.7-19)	Insulin – radioimmunoassay method (Radim Kit, Rome)	Mean ± SD	HOMA1-IR QUICKI HOMA-β %	1.49 ± 0.91 for all 1.37 ± 0.73 for M 1.65 ± 1.10 for W 0.37 ± 0.04 for all 0.38 ± 0.04 for M 0.37 ± 0.04 for W 144.1 ± 142.2 for all 130.4 ± 124.7 for M 164.6 ± 163.9 for W
			Glucose – oxidase method (no data provided)			
7. Gayoso-Diz et al., (2011)	59	1. Non-diabetic Spanish subjects 2. n = 2246 3. 1329 W and 917 M 4. Median 47 years (20-92)	Insulin – radioimmunoassay method (no data provided) Glucose – enzymatic hexokinase method (no data provided)	Median	HOMA1-IR	1.73 for all 2.06 for M 1.93 for W
8. Yamada et al., (2011)	51	1. Selected Japanese reference individuals (with NFG, BMI<25kg/m^2, ALT<31 U/L) 2. n = 2153 3. 1336 W and 817 M 4. 46.0 ± 11.0 year (20-79) years	Insulin – fluorescence-enzyme method (ST AIA-PACK IRI; Toso, Tokyo)	Reference interval according to CLSI (C28-A3) between 2.5th -97.5th percentile (RI; mean ± 2SD of log HOMA1-IR values)	HOMA1-IR	0.4 – 2.4
			Glucose – (no data provided)	Cut-off for insulin resistance identification	HOMA1-IR	≥ 2.5
9. Qu et al., (2011)	6	1. Mexican Americans 2. n=1854 3. No data provided 4. ≥18 years	Insulin – enzyme-linked immunosorbent assay/ ELISA immunoassay kit (Mercodia, Uppsala) Glucose – method – no data provided, (Glucostat analyzer (Model 27, YSI, IncYellow Springs, Ohio)	ROC curve for insulin resistance identification	HOMA1-IR	3.80
10. Oka et al., (2012)	60	1. Middle-aged Japanese with NGT 2. n = 1125 3. 697 M and 428 W 4. 51.9 ± 7.6 years (30-65)	Insulin -chemiluminescence immunoassay method (BML, Inc. Tokyo) Glucose – oxidase method (Automatic Glucose Analyzer ADAMS Glucose GA-1160, Arkray, Kyoto)	Mean (95% CI)	HOMA1-IR Matsuda ISI Disposition Index (ISSI-2)*	0.83 (0.81-0.86) 14.8 (14.1-15.4) 2.92 (2.79-3.03)
11. Würtz et al., (2012)	61	1. Young adults Finns 2. n = 7098 3. 3665 W and 3433 M 4. 31 ± 3 years (24-39)	Insulin – radioimmunoassay (Pharmacia Diagnostics)/ microparticle enzyme immunoassay kit (Abbott Laboratories)	Median (Q1-Q3)	HOMA1-IR	0.98 (0.78–1.30) for M 0.92 (0.73–1.20) for W
			Glucose – glucose dehydrogenase (Granustest 250; Diagnostica Merck)/ enzymatically (Olympus AU400)	Cut-off for insulin resistance identification on: 80th percentile	HOMA1-IR	1.3

Table 2. *Continued.*

12. Yamada et al., (2012)	62	1. Non-diabetic Japanese 2. n = 6868 3. 3141 W and 3727 M 4. 49.3 ± 11.7 years for W and 49.7 ± 12.1 years for M	Insulin – fluorescence-enzyme method (ST AIA-PACK IRI; Toso, Tokyo) Glucose – no data provided	ROC curve for MS identification	HOMA1-IR	1.70
13. Stankiewicz-Olczyk et al., (2012)	63	1. Polish professionally active men 2. n = 402 3. 402 M 4. 30-60 years	Insulin – no data provided Glucose – no data provided	Mean ± SD	HOMA1-IR QUICKI	2.49 ± 1.93 Men without MS 1.74 ± 1.16 Men with MS 3.41 ± 2.38 0.34 ± 0.03 Men without MS 0.36 ± 0.03 Men with MS 0.32 ± 0.02
14. Takahara et al., (2013)	52	1. Healthy reference Japanese subjects 2. n = 204 3. 60 W and 144 M 4. 49 ± 9 years (23-69)	Insulin – no data provided Glucose – no data provided	One-sided reference interval according to CLSI as: Mean +2SD Mean –2SD Insulin resistance identification according to CLSI, as: Mean -2SD Mean +2SD	 Matsuda Index HOMA1-IR Matsuda Index HOMA1-IR	 ≥ 4.3 ≤ 2.4 < 4.3 > 2.4
15. Kozakowski et al., (2013)	64	1. Polish PCOS women 2. n = 40 3. 40 W 4. 28.6 ± 7.6 years (19-49)	Insulin – immunoradiometric method (Immunotech SA, France) Glucose – hexokinase method (Cobas Integra 400, Roche Diagnostics)	Mean ± SD	HOMA1-IR	2.68 ± 2.4
16. Gayoso-Diz et al., (2013)	65	1. Spanish general adult population 2. n = 2459 3. 1436 W and 1023 M 4. 49.4 ± 16.2 years (20-92)	Insulin – radioimmunoassay method (Coat A Count Insulin, Los Angeles) Glucose – hexokinase enzymatic method (no data provided)	Cut-off for insulin resistance identification on: 90th percentile	HOMA1-IR	3.46
17. Timoteo et al., (2014)	66	1. Portuguese patients admitted in a Cardiology ward 2. n=1784 3. 874 W and 910 M 4. 58.1 ± 18.2 year (no data)	Insulin – electrochemiluminescence method – ECLIA (no data provided) Glucose – the glucose-oxidase method (no data provided)	Cut-off for insulin resistance identification on: 90th percentile ROC curve for MS identification	HOMA1-IR HOMA1-IR	2.33 2.41 (for n = 300)

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Table 2. *Continued.*

18. Tohidi et al., (2014)	9	1. Non-obese healthy Iranian with FSI<2.88 μU/mL, FG<3.5 mmol/L 2. n = 275 3. 167 W and 108 M 4. 34.5 ± 7.5 years for W and 41.3 ± 13.9 years for M (24-83)	Insulin – electrochemiluminescence immunoassay – ECLIA (Roche Diagnostics kit/ Cobas e-411 analyzer, Roche/Hitachi, GmbH, Mannheim) Glucose – oxidase method (no data provided)	Reference interval according to CLSI/IFCC between: 2.5th – 97.5th percentile	HOMA1-IR HOMA2 QUICKI	0.63 – 2.68 0.40 – 1.80 0.33 – 0.42
19. Skoczeń et al., (2014)	67	1. Polish children with simple obesity 2. n = 222 3. 109 W and 113 M 4. 13.1 ± 3.7 years (2-18)	Insulin – no data provided Glucose – no data provided	Mean ± SD	HOMA1-IR <10 years, 10-16 years, > 16 years	 1.6 ± 1.2 3.6 ± 4.6 2.3 ± 1.7
20. Bednarek-Tupikowska et al., (2014)	68	1. Polish adults with BMI<27 kg/m^2 2. n=342 3. 218 W and 124 M 4. 20-40 years	Insulin – Micro Particle Enzyme Immunoassay (AxSym Insulin Kit, Abbott) Glucose – oxidase method (Dade Behring Marburg GmbH)	Mean ± SD	HOMA1-IR QUICKI FIRI	Non-obese normal subjects 1.07 ± 0.43 MONW subjects 2.33 ± 0.77 Non-obese normal subjects 0.40 ± 0.05 MONW subjects 0.31 ± 0.03 Non-obese normal subjects 0.95 ± 0.35 MONW subjects 1.49 ±0.87
21. Oh et al., (2015)	69	1. Korean adults with NGT and glucose concentration <155 mg/dl in 60 minute OGTT 2. n = 149 3. 117 W and 32 M 4. 52.8 ± 7.0 years (30-80)	Insulin – no data provided Glucose – no data provided	Mean ± SD	Disposition Index (ISSI-2) HOMA1-IR HOMA-β-cell Matsuda Index	301.2 ± 113.7 1.2 ± 0.6 102.7 ± 52.9 9.3 ± 4.9
22. González-Zavala et al., (2015)	70	1. Mexican adolescents in different pubertal stages 2. n = 292 3. 152 W and 140 M 4. 13.02 ± 0.94 years (12-15)	Insulin – immunofluorescence assay with labeled substrate – IFALS (TOSOH AIA-600, Tokyo) Glucose – hexokinase enzymatic method (InCCA – Intelligent Clinical Chemistry Analyzer, Diconex)	Mean ± SD	HOMA1-IR	2.9 ± 2.5 – all subjects 2.3 ± 1.3 – Prepubertal 2.8 ± 2.4 – Middle pubertal 3.3 ± 3.0 – Postpubertal

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Table 2. *Continued.*

23. Santos et al., (2016)	17	1. Chilean NGT adults with FPG <100mg/dL and 2-h glucose OGTT levels <140 mg/dL 2. n = 1393 3. 1178 W and 215 M 4. 36.5 ± 11.1 years (18–60)	Insulin -electrochemiluminescence immunoassay (no data provided) Glucose – colorimetric glucose-oxidase method (no data provided)	Mean ± SD	ISSI-2 * Matsuda ISI-COMP index HOMA-S index	2.73 ± 1.10 4.7 ± 2.8 63.8 ± 39.1
24. Kwon et al., (2017)	71	1. Young healthy Korean 2. n = 8707 3. 4515 W and 4192 M 4. 45.63 ± 0.23 M, 44.31 ± 0.21 W years, (20-39)	Insulin – radioimmunoassy (Gamma counter; Hewlett Packard, USA/ 1470 WIZARD gamma-counter (PerkinElmer) Glucose – method – no data provided; ADVIA 1650, (Siemens, USA)/ Hitachi 7600 (Hitachi)	Cut-off for insulin resistance identification on: 75th percentile	HOMA1-IR	2.18 for W 2.19 for M
25. Płaczkowska et al., (2019)	72	1. Polish young adults 2. n=130 3. 106 W and 24 M 4. Median age 23 years (Q1-Q3: 21-24) (18-31)	Insulin – enzyme-linked immunosorbent assay (ELISA, DRG Diagnostics) Glucose – GOD/POD method (Thermo Electron Oy, Vantaa)	One-sided reference interval according to CLSI as: 95th percentile 5th percentile Cut-off for insulin resistance identification on: 75th percentile 25th percentile	HOMA1-IR HOMA2 QUICKI Matsuda ISSI-2 HOMA1-IR HOMA2 QUICKI Matsuda ISSI-2	≤4.00 ≤2.27 ≥0.31 ≥3.19 ≥206 > 2.78 > 1.72 < 0.33 < 4.31 < 261

ALT – Alanine aminotransferase, BMI – Body Mass Index, CLIA – Chemiluminescent method, CLSI – Clinical and Laboratory Standards Institute, ECLIA – Electro-Chemiluminescence Immunoassay, ELISA – Enzyme-Linked Immunosorbent Assay, FG – Fasting Glucose, FIRI – Fasting Insulin Resistance Index, FSI – Fasting Serum Insulin, GOD/POD – Glucose oxidase (GOD) and Peroxidase (POD) method, HOMA-IR – Homeostatic Model Assessment of Insulin Resistance, IFCC – International Federation of Clinical Chemistry and Laboratory Medicine, IRMA – Immunoradiometric method, ISSI-2 – Insulin Secretion-Sensitivity Index-2, M – men, MONW – Metabolically Obese Normal Weight, MS – metabolic syndrome, NGT – Normal Glucose Tolerance, NFG – Normal Fasting Glucose, OGTT – oral glucose tolerance test, Q1-Q3 – Interquartile Range, RI – Reference Interval, QUICKI -Quantitative Insulin Sensitivity Check Index, ROC – Receiver Operating Characteristic Curve, SD – standard deviation, W – women.
* the ratio of AUC insulin/glucose was calculated by traditional unites, μIU/mL and mg/dL, respectively

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is defined mostly at 2.5 which results in an elevated frequency of insulin resistance, as we have seen also in our own research. Therefore, it is of paramount importance to determine a laboratory's reference intervals to properly identify insulin resistance[41].

The concept of reference range and methods of reference interval establishment

The determination and introduction of common use reference intervals for IR indices is crucially important to doctors, general practitioners and other medical staff for better assessment of patients' clinical conditions and the application of appropriate therapeutic actions. The idea of reference intervals is based on the general concept of reference range, and the procedure used to carry it out is complex and multi-faceted[43]. The concept of reference range was launched by the Finnish researchers Ralph Gräsbeck and Nils-Erik Saris[44,45] and based on comparison of the patients' results with a set of values used as reference, obtained on the basis of a well-described and standardized laboratory procedure. According to this concept, in order to establish reference ranges, it is necessary to provide: i) study population characteristics, the method of selecting subjects and assessing their health status; ii) criteria for the selection of subjects, their physiological condition, method of preparation for the study and procedure of collecting specimens; iii) the manner in which samples were handled and a description of the measurement, calculation and applied statistical methods[46,47].

In 1969, the International Federation of Clinical Chemistry (IFCC) convened an Expert Panel on the Theory of Reference Values (EPTRV), in order to systemically develop the concept launched by Gräsbeck and Saris. EPTRV's tasks were to develop a procedure recommended for determining reference values, to analyse the obtained results and to establish appropriate nomenclature for their presentation[48]. The introduced terminology, intended for widespread use, is presented in Table 1. It includes the definitions and methods of determining reference intervals developed by the National Committee for Clinical Laboratory Standards (NCCLS), published in a document called C28-A3 in 2008 (ref.[49]).

The protocol presented in Table 1 refers to the *a priori* approach of selecting individuals for reference groups. This method consists in collecting data about a potential reference individual by means of a personal information questionnaire and health assessment, and the selection or exclusion of that subject. The last step, performed after all of the above procedures, is collecting the specimens. However, the second method of selecting reference individuals is the *a posteriori* approach, where the process of accepting the subject as a reference individual usually takes place after the collection of samples and laboratory examination. Both methods described above are referred to as direct sampling, which the IFCC recommends in the first instance for the determination of reference intervals. The *a posteriori* method could be also used for indirect methods of reference interval establishment based on previously collected data, known as data mining, which are especially useful for groups such as neonates and children[47,50].

The reference intervals and cut off values for insulin resistance in different populations

The majority of scientific studies provide information about insulin resistance indices values, given as mean or median, but only a few publications concern the determination of reference intervals according to the Clinical and Laboratory Standards Institute (CLSI) protocol and/or cut-off values for these indicators[9,51,52]. The most common values of insulin resistance indices used for the identification of these disturbances present in the scientific literature are established as upper 75th or 95th, or below 25th or 5th percentile values observed in the different examined populations. This is not exactly in accordance with laboratory guidelines, but is very widely applied in the scientific literature. In Table 2 the values of indices used to diagnose insulin resistance (HOMA1-IR, HOMA2, HOMA2 C-peptide, QUICKI), insulin sensitivity (Matsuda Index) and beta cell condition (ISSI-2), based on different decision-making factors, are presented in time order. We tried to present the most recent and different population studies in Table 2, and our aim was to show the variation in observed values rather than cite the results of all available studies.

As we show in Table 2, determination of cut-off values was applied not only to identify people with IR in the general population, but more frequently to differentiate populations with an increased risk of metabolic disorders associated with insulin resistance. This is understandable because IR is one of the most important factors in civilization diseases, such as DM, MS and CVD, as well as kidney failure[73-76]. Hence, knowledge of laboratory limitations and population differences in IR indices determination is important for the proper use of IR indices in making adequate clinical decisions. According to Table 2, the values for indirect insulin resistance indicators are different for different ages, sexes, populations and ethnic groups. The observed differences in the values of insulin resistance indices between different populations are related to ethnic heterogeneity[77,78]. One of the reasons for this situation may be the difference in the amount and distribution of body fat, body mass and height affecting BMI among the studied groups (i.e. Asians and Caucasians). According to our research results (in press) for young Caucasian (aged 18-31) the reference intervals for indirect insulin resistance indices which we examined according to CLSI protocol were: ≤4.00, ≤2.27, ≤4.10, ≥0.31 for HOMA1-IR, HOMA2, HOMA2 C-pep., and QUICKI respectively. For insulin sensitivity the value of Matsuda Index was established as ≥3.19 and for beta cell pancreatic function ISSI-2, as ≥206. The cut-off values for insulin resistance recognition were established as 75th percentile: >2.78, >1.72, >2.63, <0.33 for HOMA1-IR, HOMA2, HOMA2 C-pep., QUICKI respectively and <4.31 and <261 as 25th percentile for Matsuda and ISSI-2, respectively[72]. In the scientific literature, various values of IR indicators are observed, not only due to individual or population vari-

ability, but also the laboratory methods used to determine glucose and insulin concentrations.

The usefulness of HOMA indices are discussed in the literature and even the authors themselves indicate their limitations. Among others authors, Song et al. state that especially HOMA-IR, is independently and consistently associated with diabetes risk in a multiethnic cohort of U.S. postmenopausal women and using them could provide a benefits from early intervention in diabetes' high risk groups identified on the basis of HOMA indices[79]. At the same time Sung et al. criticized use HOMA-B% for predicting diabetes in Korean women as useless, but they showed very good predictive values for HOMA1-IR and fasting glucose concentration to predicting diabetes[80]. Nearly twenty years after first describing in 2004, Wallace, Mathews et al. summaries utility of HOMA modeling in clinical and epidemiological studies. They maintained the opinion about usability HOMA derivate indices in predicting diabetes development, but also indicated ethnicity, reproducibility and reporting HOMA-B% in isolation as the weak points of the model[12].

On the basis of this study, it can also be observed that the presented reference intervals, decision values or cut-offs for insulin resistance indices are determined in various ways, but it is rare that they meet the criteria of the CLSI and/or IFCC recommendations. It should be emphasized that the CLSI document used to establish reference intervals, and even recommended for laboratory practice, is still not widely used in laboratory medicine.

However, currently the lack of an international standard for insulin laboratory determination, the use of different analytical methods, and the non-use of the CLSI protocol to receive reference intervals for indirect insulin resistance indicators all have a direct, limiting impact on the use of these parameters in an epidemiological context in routine medical practice. This is of particular importance to children and to adolescents, due to hormonal changes and the increase in and distribution of adipose tissue, parameters related to insulin resistance change.

Before introducing specific decision limits for the diagnosis of IR in clinical practice, appropriate reference values for indirect indices should be determined, and if this is not possible, data from studies carried out in the most ethnically, socio-economically and age-matched populations should be applied. The uncritical use of literature data without taking into account the values characteristic of the analyzed population may result in erroneous clinical decisions.

CONCLUSION

A comparison of insulin resistance and the sensitivity and efficiency of pancreatic β cell values in different populations is difficult, due to significant differences in the results obtained by different analytical methods and the use of various criteria for inclusion and exclusion from the reference group. Hence, the decision-making factors for insulin resistance recognition should be applied judiciously, and the setting of certain recommended values for given populations and age groups is an urgent requirement.

In order to improve the diagnostic process for insulin resistance, population studies should be performed and the reference intervals and cut-off values for insulin resistance, insulin sensitivity and pancreatic β cell function should be determined for different age groups, in accordance with CLSI protocol, and the standardization of laboratory methods of insulin measurement is indispensable. With regard to the enormous prevalence of diseases of civilization connected with insulin resistance, the issue of appropriate determination and knowledge of insulin resistance reference limit values by general practitioners is especially important for effective and accurate diagnosis and therapeutic measures.

Search strategy and selection criteria

Scientific articles from the period 1968 to 2018 were searched using the PubMed, SCOPUS and Google Scholar databases. Search terms included: insulin resistance, insulin resistance indicators, reference interval and decision limit. We wanted to assess the diversity in the range of indirect insulin resistance indices resulting from clinical trends, different laboratory methods and different populations and evaluated the proposed decision values and reference intervals.

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