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Challenges in the diagnosis of insulin resistance: Focusing on the role of HOMA-IR and Tryglyceride/glucose index

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ABSTRACT

Background and aims: Metabolic Syndrome (MS) prevalence is increasing worldwide in line with the growing prevalence of obesity. The underlying mechanism of MS is insulin resistance which can be diagnosed by measuring Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Triglyceride/Glucose (TyG) Index. This review will focus on comparing studies assessing the HOMA-IR and TyG index cut-off points.
Methods: We carried out a comprehensive review of the literature using suitable keywords on the search engines of PubMed, Scopus, Research Gate, and Google Scholar in the month of October 2020.
Results: There is a high degree of variability in determining threshold levels of HOMA-IR for defining insulin resistance. The distribution of the HOMA-IR varies according to the demographic characteristics of the subjects, such as age, sex, and race, making it difficult to estimate the optimal cut-off point. Another simpler method without requiring the use of insulin assays is TyG Index. Similar to HOMA-IR, the TyG Index cut-off point from existing data shows varying results.
Conclusion: The HOMA-IR and the TyG index are simple and widely used methods for determining insulin resistance. However, an issue that arises is determining the insulin resistance cut-off point for both methods. Further studies are needed to assess the cut-off point of insulin resistance for various ethnicities associated with the risk of developing MS later in life.

1. Introduction

Insulin resistance is a condition associated with an increased risk of cardiovascular disease and type 2 diabetes mellitus (T2DM). Clinically, insulin resistance is known as syndrome X, or insulin resistance syndrome, and now known as metabolic syndrome (MS). MS is a group of interrelated, multidimensional factors that can increase the risk of cardiovascular disease and T2DM [1]. The prevalence of MS is steadily rising, in line with the growing prevalence of obesity globally [2,3].

MS occurs due to insulin resistance, namely the inability of exogenous or endogenous insulin to perform its role in glucose uptake and utilization [4,5]. Early detection of insulin resistance is important so that treatment can be carried out as early as possible. Hyperinsulinemic euglycemic clamp (HEC) is the gold standard for assessing insulin resistance, but due to the complexity of the method, this test is only used in small-scale research and not for

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population studies. A simpler method that can be used for clinical purposes and has been validated is the homeostasis model assessment of insulin resistance (HOMA-IR). HOMA-IR is strongly correlated with the results of the HEC examination, with a good correlation coefficient value. HOMA-IR is a model of the relationship between glucose and insulin dynamics under fasting conditions to predict insulin resistance, simplified by the formula: fasting insulin (μU/dL) × fasting blood glucose (mmol/L)/22.5 [6,7]. There are several ways in which the HOMA-IR cut-off values for insulin resistance can be determined. The first approach is based on a healthy population's 75th percentile or 90th percentile values [8–10].

The second approach is considered the better approach, as it relates to the clinical findings of insulin resistance, such as in MS. Several authors have used receiver operating characteristic (ROC) curves for estimating the cut-off point. In previous studies, the Youden index and the distance from the upper left corner of the ROC curve are the two best methods used to determine the HOMA-IR cut-off point. Several studies to determine the HOMA-IR cut-off point have been conducted in various geographic areas with varying results resulting from ethnic variations and different approaches used to determine the cut-off point [10–13].

Several studies have shown that insulin resistance occurs at a lower degree of central obesity in Asia. The HOMA-IR cut-off value for insulin resistance is also generally lower [14]. Insulin resistance can also be assessed using the quantitative insulin sensitivity check index (QUICKI), Matsuda index, McAuley index, Belfiore, Cederholm, Avignon, and Stumvoll [7].

Methods mentioned previously to assess insulin resistance require an assessment of insulin levels, which is not practical in clinical practice in the community. A simpler method reported to be correlated with the HOMA-IR value is the triglyceride-glucose index (TyG). TyG index is calculated by using the equation Ln [fasting triglyceride (mg/dL) x fasting glucose (mg/dL)/2]. By using serum triglyceride testing instead of insulin testing, this method is likely to be more feasible in resource-limited countries.

As such, this review will address alternative methods of measuring insulin resistance, focusing on comparing studies assessing the HOMA-IR cut-off point and TyG index, both evaluated clinically by the presence or absence of MS or by using percentiles.

1.1. Epidemiology of metabolic syndrome

MS is commonly known as insulin resistance syndrome. Insulin resistance is the inability of exogenous or endogenous insulin to perform its role in glucose uptake and utilization in normal population [4,5]. An impaired biological response to insulin stimulation in target tissues, especially the liver, muscle, and adipose tissue, occurs. Insulin resistance can be caused by genetic factors that regulate the insulin cascade and acquired factors such as age, lack of physical activity, nutritional imbalance, high adipose tissue, and certain medications. Higher insulin levels are needed to achieve glycemic control and prevent ketosis in these conditions, such that hyperinsulinemia occurs as compensation [15,16].

The clinical definition of insulin resistance is difficult to define because of the absence of specific parameters. Clinically, insulin resistance is associated with its metabolic consequences, such as hyperglycemia, hypertension, dyslipidemia, and endothelial dysfunction. This is collectively known as MS, insulin resistance syndrome, or syndrome X. Insulin resistance also increases clotting and serum uric acid. These metabolic disorders are interrelated in their ability to increase the risk of cardiovascular disease and T2DM [1,15,16].

The prevelance of MS is found to be three times as much compared to diabetes. The global prevalence of MS can be estimated at more than one billion globally [17]. The International Diabetes Federation (IDF) estimates that around 25% of the world's population has MS. According to Kaur et al. [18], the worldwide prevalence of MS is between 10% and 84% depending on ethnicity, age, sex, and race of the population [18–20]. Studies by Pal and Ellis [21] showed that 20% of adults in the Western world suffer from MS [20,21]. Notably, despite these differences, MS increases in accordance with an increase in BMI [2,3,21]. The growing prevalence of MS consequently results in an increased risk of T2DM and cardiovascular disease. Moreover, when components of MS coincide simultaneously, severe cardiovascular disease may result [1,15,16].

The World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP) III, American Association of Clinical Endocrinologists (AACE), and IDF acknowledge the increased risk of T2DM and cardiovascular disease in MS; however, there is debate over the definition of the MS components. These organizations have all developed criteria for defining MS by considering the appropriate variables to accurately identify people at a higher risk of developing T2DM and cardiovascular disease [20]. These differences contribute to the variation in the prevalence of MS.

To consolidate these differences, in 2008, the IDF, American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (AHA/NHLBI), World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity devised criteria for diagnosing MS. Patients are diagnosed with MS when at least three of the five criteria are met: Increased waist circumference based on the definition of each country, increased triglycerides (>150 mg/dL or the use of triglyceride-lowering drugs), decreased HDL (<40 mg/dL for men; <50 mg/dL for women; or the use of HDL-lowering drugs), hypertension (systolic blood pressure ≥130 mmHg and/or diastolic ≥85 mmHg; or the use of antihypertensive therapy), and increased fasting blood sugar (≥100 mg/dL or the use of blood sugar-lowering drugs) [22]. However, a criterion for MS that differs in each population is the criteria for central obesity based on the increase in abdominal circumference [22]. Interestingly, studies also show that racial differences within a country appear to require different cut-off points [23].

1.2. Diagnostic criteria for insulin resistance

The gold standard for measuring insulin resistance is the HEC technique by DeFronzo et al., [24], in which the plasma insulin concentration is raised acutely and maintained at approximately 100 mU/mL by intravenous insulin drip. The plasma glucose concentration is kept constant at a basal level by glucose infusion using the negative feedback principle. Under euglycemia conditions, the rate of glucose infusion equals the uptake of glucose by all tissues in the body and is a measure of tissue sensitivity to exogenous insulin [24]. The application of this technique is limited in clinical use. Similarly, other indices such as the McAuley, Belfiore, Cederholm, Avignon, and Stumvoll indexes are more widely used for epidemiological purposes (Table 1) [7].

Nonetheless, clinically useful surrogate indices for insulin resistance are HOMA-IR, HOMA2, QUICKI, TyG index, triglyceride/HDL ratio, and Matsuda index (Table 2). Of all these indices, HOMA-IR is an index that is often used in clinical practice. Additionally, several studies have shown that the TyG index can also be used in clinical practice because it is simpler.

2. HOMA-IR

HOMA-IR is a simple, validated method that can be used for

Table 1
Methods of measuring insulin resistance for research [7].

Method	Formula
HEC	$lSI_{HEC} = MCR/I_{mean}$ $MCR = M_{mean}/(G_{mean} \times 0.18)$
McAuley Index	$_e(2,63 - 0,28\ \ln(I_0) - 0,31\ \ln(TAG_0))$
Belfiore Index	$2/lSI_{Be1fiore} = \frac{G_S}{G_N} \times \frac{I_S}{I_N} + 1$
Avigson Index	$Sib = 10^8/\begin{pmatrix} I_0(mU/l) \times G_0 \\ (mmol/l) \times VD \end{pmatrix}$ $Si2h = 10^8/\begin{pmatrix} I_{120}(mU/l) \times G_{120} \\ (mmol/l) \times VD \end{pmatrix}$
Stumvoll Index	$0.156 - 0.0000459 \times I_{120}(pmol/L) - 0.000321 \times I_0(pmol/L) - 0.00541 \times G_{120}(mmol/L)$
Gutt Index	$75,000 + (G_0 - G_{120})\ (mg/dl) \times 0.19 \times BW/120 \times G_{mean}$ $(0\ ,120)\ (mmol/L) \times Log$ $[I_{mean}(0,\ 120)]\ (mU/L)$

HEC, *hyperinsulinemic euglycemic clamp*; ISI, *insulin sensitivity index*; MCR, *metabolic clearance rate*; I, insulin; M, *metabolized glucose;* G, *blood glucose concentration;* I_0, *fasting insulin*; TAG_0, *fasting triglyceride;* G_S and G_N, glucose concentration with TTGO jam ke-0 dan ke-2; VD, *volume of distribution* (150 mL/kgBB); BW, *body weight.*

Table 2
Clinical Insulin Resistance Measurement Methods [7,25,26].

Method	Formula
HOMA-IR	I_0 x G_0/22.5
HOMA-2	*Computer model* from HOMA
QUICKI	$1/\begin{bmatrix} \log(I\mu U/mL) \\ +\log(Gmg/dl) \end{bmatrix}$
TyG Index	TAG_0/G_0
TG/HDL Ratio	TAG/HDL
Matsuda Index	10,000/sqrt (G_0 x I_0 x G_{120} x I_{120})

HOMA-IR, *Homeostasis Model Assessment of Insulin Resistance*; QUICKI, *quantitative insulin sensitivity check index*; TyG, Triglyceride/Glucose; TG, triglyceride; HDL, *High-Density Lipoprotein*; TAG_0, *fasting triglyceride*; I_0, *fasting insulin*; G, *blood glucose concentration*.

clinical purposes. HOMA-IR was initially developed in 1985 by Matthews et al., [27], it is a model of the interaction dynamics between glucose and insulin. HOMA-IR is used to predict fasting glucose and fasting insulin concentrations under stable conditions, allowing various conditions of insulin resistance and pancreatic cell β function to be observed [27–29]. This method measures insulin resistance by assuming feedback between the liver and β cells. Glucose concentration is regulated by insulin-dependent glucose production in the liver, whereas insulin levels depend on the response of pancreatic β cells to glucose concentrations. Therefore, a reduced response to glucose-stimulated insulin secretion reflects a deficiency in β cell function. Insulin resistance can be observed by the reduced suppressive effect of insulin on glucose production in the liver. The HOMA formula is a simplification of the mathematical model, namely: HOMA = {[fasting insulin (U/mL)] × [fasting glucose (mmol/L)]}/22.5. The denominator in this formula was obtained from the normal value of fasting insulin of 5 U/mL and glucose of 4.5 mmol/L [7,14,29,30].

HOMA-IR is currently widely used because it is strongly correlated with HEC, the gold standard for measuring insulin resistance. Various studies have shown a strong correlation between HOMA-IR and HEC (Table 3).

Table 3
HEC and HOMA correlation studies.

Study	HEC correlation with HOMA	*p*
Matthews et al. [27]	RS = 0,88	0,0001
Bonora et al. [31]	RS = 0,82	0,0001
Emoto et al. [32]	*r* = 0,73	0,0001
Katsuki et al. [33]	*r* = 0,73	0,0001

HEC, Hyperinsulinemic euglycemic clamp; HOMA, *Homeostasis Model Assessment*.

There is a high degree of variability in determining threshold levels of HOMA-IR for defining insulin resistance. Until now, no consistent cut-off point exists. Previous population studies to determine the HOMA-IR cut-off point have been carried out in different populations with varying results [14]. Inconsistencies among studies result from different criteria for determining insulin resistance and different approaches for determining threshold values.

There are two ways to determine the HOMA-IR threshold points. The former approach uses a specific percentile, such as the 95th or 75th in the normal population as recommended by Reaven in The First Annual World Congress on the Insulin Resistance Syndrome. The normal population is a population without metabolic disorders [34–36].

The second approach is to use ROC curves derived from particular populations. This approach requires determining a suitable population to serve as a reference or control (healthy individuals), while the remaining individuals constitute the appropriate “sick” population, for example, an MS population. These two components constitute the construction of the ROC curve and the selection of a valid cut-off value based on sensitivity, specificity, and other indices [8,9,34,37].

However, the distribution of the HOMA-IR varies according to the demographic characteristics of the subjects, such as age, sex, and race, making it difficult to estimate the optimal cut-off point using the percentile criteria (Tables 4 and 5) [13]. For example, the 75th percentile of the HOMA-IR is 2.53 for healthy Koreans, 1.6 for healthy Iranians, 2.0 for healthy Swedish men, and 3.8 for French men [8,38–41]. Further, it is unclear whether the proposed cut-off value of HOMA-IR based on the percentile criteria can predict clinically relevant outcomes. As such, using the ROC curve may be better [14,30,39,42].

The variability of the HOMA-IR cut-off value is very high because MS is strongly influenced by the subject's ethnicity, method of analysis, criteria for diagnosing MS, and metabolic conditions of the population. There are several criteria to determine MS, such as IDF, ATPIII, WHO, or AACE and each study used different criteria. HOMA-IR distribution also varies according to population race. From the various studies that have been described (Table 6 and Table 7), the cut-off point for Caucasians is relatively higher than for Non-Caucasians (Japan, Thailand, and Korea). It can be caused by the HOMA-IR formula which is derived from a mathematical model of insulin and glucose physiology from insulin signaling pathway, in contrast to liver function impairment. HOMA-IR might not appropriate for lean populations such as Asians and populations with

Table 4
Summary of studies of HOMA-IR cut-off point with percentile method in various populations.

Study	Population	HOMA-IR Cut-off Point	Criteria
Do et al. (2010) [45]	Thailand	1,55	Percentile 90
Esteghamati et al. (2009) [8]	MS-IDF	1,6	Percentile 75
	MS-ATPIII	1,8	Percentile 80
		2,3	Percentile 90
Sumner et al. (2008) [43]	United States of America	2,73	Percentile 66
Geloneze et al. (2006) [46]	Brazil	2,77	Percentile 90
Miccoli et al. (2005) [44]	Italy	2,77	Percentile 80
Marques-Vidal et al. (2002) [40]	France	3,8	Percentile 75
Nakai et al. (2002) [13]	Japan	1,7	Percentile 90
Hedblad et al. (2000) [41]	Sweden	2	Percentile 75

HOMA-IR, *Homeostasis Model Assessment of Insulin Resistance*; MS-IDF, *metabolic syndrome -International Diabetes Federation*; MS-ATPIII, *metabolic syndrome -Adult Treatment Panel*.

Table 5
Summary of studies of HOMA-IR cut-off point with ROC method on various populations.

Study	Population	HOMA-IR Cut-off Point	Criteria
Yun K-J (2016) [49]	Korea		
	Male	2,23	ROC
	Pre-menopausal female	2,39	ROC
	Post-menopausal female	2,48	ROC
Timoteo et al. (2014) [52]	Portugal	2,41	ROC
Yamada et al. (2012) [51]	Japan	1,7	ROC
Lee JG et al. (2009) [48]	Korea		
	Male	1,22	ROC
	Female	1,28	ROC
Esteghamati (2009) [8]	Iran	1,8	ROC
	Age 38±12 years, non-diabetes normotensive	1,95	ROC
Tome et al. (2009) [50]	Spain	2	ROC
Lee S et al. (2006) [47]	Korea	2,34	ROC

HOMA-IR, *Homeostasis Model Assessment of Insulin Resistance;* ROC, *receiver operating characteristic*.

Table 6
TyG Index Cut-off Value based on Percentile Method from Other Studies.

Study	Population	TyG Index Cut-off Point	Criteria
Unger et al. (2014) [63]	Argentina	8,6	Percentile 75
		8,9	Percentile 90

TyG, *Triglyceride/Glucose*.

Table 7
TyG Index Cut-off Point Value based on ROC Method from Various Studies.

Study	Population	TyG Cut-off Point	MS Criteria
Unger et al. (2014) [64]	Argentina	8,8	AHA/NHBLI
Aulia et al. (2014) [62]	Indonesia	4,76	NCEP/ATPIII
Khan (2018) [54]	Pakistan	8,91	IDF
Li (2018) [55]	China	8,706	NCEP/ATPIII
		8,697	IDF

TyG, *Triglyceride/Glucose;* ROC, *receiver operating characteristic;* AHA, *American Heart Association*; NHBLI, *National Heart, Lung, and Blood Institute;* IDF, *International Diabetes Federation;* NCEP, *national cholesterol education program*; ATPIII, *Adult Treatment Panel*; MS, *metabolic syndrome*.

lower beta-cell function and insulin secretion defects [53]. Yun, et [49] al and Lee JG et al. [48] in their studies showed higher HOMA-IR cut-off values for women. Differences in insulin sensitivity between men and women may be due to differences in adipose tissue, muscle mass, hormones, and body fat distribution (subcutaneous and visceral fat) [49].

2.1. TyG index

The HOMA-IR and the insulin testing methods described previously require laboratory data on insulin levels, which is difficult to perform in daily clinical practice due to their inability to be carried out in countries with limited resources. Another simpler method without requiring the use of insulin assays is the TyG Index. This method requires only simple laboratory parameters, such as triglycerides and glucose, which can be measured without a great financial expense [54].

TyG index is a marker for predicting MS. According to a study by Li et al. [55] in China, the area under the curve (AUC) of the TyG index is 0.802 (95% CI 0.774–0.831, p-value = 0.004) in the MS population using the ATP III criteria [55]. The TyG index has been shown to correlate with HEC in assessing insulin sensitivity, so it can be useful to determine insulin resistance among subjects with varying glucose tolerance and body weight [56]. The TyG index also reportedly correlates with HOMA-IR and can be used as a marker of insulin resistance [57–60]. The TyG index is obtained by using the equation Ln[triglyceride (mg/dL) x fasting glucose (mg/dL)/2] [54].

A study by Khan et al., [54], in 2018 on subjects with and without MS (based on the IDF criteria) showed that the AUC TyG index of 0.764 (95% CI 0.700–0.828, p-value 0.001) was better than HOMA-IR which was 0.619 (95% CI 0.545–0.694, p-value 0.001) [54]. Another study reported the diagnostic value of the TyG index using the ROC method at a certain optimal cut-off point, then compared it with HOMA-IR. At the cut-off point of the TyG index, Ln is 4.65 with a sensitivity of 84% and a specificity of 45%, which is better than HOMA-IR [61]. Similar to HOMA-IR, the TyG index cut-off point from existing data shows varying results (Tables 6 and 7). A study on the cut-off point of the TyG Index for insulin resistance in Indonesia by Aulia et al. [62] in hospital employees in the Dr. Sardjito Hospital in Yogyakarta in 2014 was 4.76, with a diagnostic sensitivity of 43% and a diagnostic specificity of 85% [62].

The TyG index cut-offs also varied between the existing studies.

TyG Index also shows an insulin resistance state but with a different pathway compared to HOMA-IR. Triglycerides increase free fatty acids, resulting in increased transfer of free fatty acids from adipose to non-adipose tissue, which causes insulin resistance. Hypertriglyceridemia causes high free fatty acid transport to the liver resulting in high hepatic glucose output. High levels of triglycerides in the liver and muscles can interfere with glucose metabolism in each target organ. A study by Lee EY et al. [25] found that the components of MS, which were hypertension, central obesity, or low HDL cholesterol levels were found more in the high TyG Index tertile. The TyG index is also better used to predict the metabolic status of patients; for example, there are atypical metabolic characteristics in obese patients. A person with obesity usually has insulin resistance and lipoprotein metabolism disorders, such as high levels of lipoprotein rich in triglycerides, cholesterol, and apolipoprotein B in plasma. However, a healthy but obese person can have dyslipidemia and insulin resistance without impaired glucose tolerance. It was also found that impaired insulin secretion can lead to progressive glucose intolerance without insulin resistance [56].

3. Summary

HOMA-IR and TyG index can indicate an insulin resistance conditions associated with several metabolic diseases that increase the risk of cardiovascular disease. Early detection of insulin resistance can be done by using the clinical criteria for MS or measuring the insulin resistance index. From various existing methods, HOMA-IR and TyG index are simple and widely used. However, an issue is determining the insulin resistance cut-off point for both HOMA-IR and TyG because of ethnic differences and methods of determination. Further studies are needed to assess the cut-off point of insulin resistance for various ethnicities associated with the risk of developing MS later in life.

In addition, based on it's cost-effectiveness, the TyG index is more suitable for developing countries due to its lower cost since it only requires data on triglyceride and glucose. Meanwhile, HOMA-IR requires glucose and insulin concentration test which are more expensive. This review has some limitations: First, there are gaps in literature searching that made it not systematic enough and were not meta-analyzed; next, the influence of the authors' personal viewpoints might lead to potential bias.

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Author's contribution

Study design and idea: Dicky Levenus Tahapary, Livy Bonita Pratisthita; Data Collection: Livy Bonita Pratisthita; Data Analysis: Livy Bonita Pratisthita, Dicky L. Tahapary, Dyah Purnamasari; Manuscript Writing: Livy Bonita Pratisthita, Nissha Audina Fitri, Cicilia Marcella; Writing supervision: Dicky L. Tahapary, Dyah Purnamasari, Tri Juli Edi Tarigan, Dante Saksono Harbuwono; Funding: Dicky L. Tahapary.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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