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Research Article
First-Degree Family History of Type 2 Diabetes Mellitus Strengthens the Agreement Between MetS-IR and HOMA-IR in Non-Diabetic Adults

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Abstract

Background and Objective: Insulin resistance is a primary factor in the pathophysiology of Type 2 Diabetes Mellitus (T2DM). Consequently, there is a significant need in clinical practice for rapid and cost-effective methods to assess this condition. The Metabolic Score for Insulin Resistance (MetS-IR) has been developed as an alternative to the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Given that individuals with a first-degree family history of T2DM are at a higher risk of developing insulin resistance, this study aimed to analyze the agreement between MetS-IR and HOMA-IR in non-diabetic adults with both a general and a first-degree family history of T2DM. **Materials and Methods:** This is an observational analytic study using a cross-sectional design, initially including 102 non-diabetic adult subjects. The analysis was focused on a sub-population of 51 subjects who had T2DM family history. Fasting glucose, fasting insulin, triglycerides (TG) and HDL-C levels were measured to calculate both MetS-IR and HOMA-IR values. A MetS-IR cut-off value of 32.83, derived from the analysis of the total population (n = 102), was used for categorization. The agreement between MetS-IR and HOMA-IR was assessed using the Kappa test. **Results:** The data analysis focused on 51 subjects with a family history of T2DM. Of this group, 36 subjects (70.59%) had a first-degree family history of type 2 diabetes mellitus (T2DM). The agreement test for the 51 subjects with a family history of DM yielded a Kappa value of 0.490 (p = 0.001), indicating moderate agreement. Further analysis of the sub-population with a first-degree family history (n = 36) revealed an increased Kappa value of 0.649 (p = 0.001), reflecting substantial agreement. **Conclusion:** A higher agreement between MetS-IR and HOMA-IR was observed in the analysis of the sub-population with a first-degree family history of T2DM. Nevertheless, based on this study's findings, the MetS-IR index cannot yet replace HOMA-IR for the detection of insulin resistance.

Key words: First-degree family, MetS-IR, HOMA-IR, insulin resistance, T2DM

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Insulin resistance is a condition defined by the decreased ability of insulin to act effectively on its target tissues, primarily muscle, liver and adipose tissue. This condition is a major component in the pathophysiology of Type 2 Diabetes Mellitus (T2DM) development[1-3]. The global prevalence of insulin resistance varies widely, ranging from 15.5 to 46.5%. A meta-analysis in the Southeast Asian Region reported an insulin resistance prevalence of 44.3%, with the rate in Indonesia reaching 42.4%. Given that insulin resistance can precede the onset of T2DM by as much as 10 to 15 years, early detection is crucial for preventing future complications[4].

Several risk factors can increase the likelihood of developing insulin resistance, such as obesity, a sedentary lifestyle and a high-carbohydrate diet[5]. A family history of T2DM is a primary contributor, with a parental history of the disease significantly increasing the risk of insulin resistance in non-diabetic individuals. In fact, this risk can increase up to 10.3-fold for individuals with a first-degree family history of T2DM compared to those without. This highlights the significant role that genetic factors play in the predisposition to insulin resistance[5,6].

The gold standard for assessing insulin resistance is the hyperinsulinemic-euglycemic clamp (HEC) method. However, the HEC is impractical for routine clinical use or large-scale population studies due to its complex, invasive and costly procedure. As an alternative, the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) has been widely used. HOMA-IR indirectly measures insulin resistance using fasting glucose and insulin levels. Despite being more practical, HOMA-IR has its own limitations, primarily because serum insulin measurement is not widely available and is relatively expensive[1,7,8].

Non-fasting insulin-based indices have been developed to overcome these limitations, one of which is the Metabolic Score for Insulin Resistance (MetS-IR). MetS-IR is a simple method calculated using routinely examined parameters, namely fasting glucose, triglycerides (TG), High-Density Lipoprotein Cholesterol (HDL-C) and body mass index (BMI)[8]. If a high degree of agreement with HOMA-IR is found, MetS-IR has the potential to become a simpler and more cost-effective screening tool for insulin resistance.

Research on the agreement between MetS-IR and HOMA-IR in the non-diabetic adult population in Indonesia, particularly within groups with a family history of T2DM, has not yet been conducted. Therefore, this study aimed to analyze the agreement between MetS-IR and HOMA-IR values in non-diabetic adults, with a focus on sub-populations possessing a family and first-degree family history of T2DM.

MATERIALS AND METHODS

Ethical statement: This study was conducted in accordance with ethical research principles and was approved by the Research Ethics Committee of The Faculty of Medicine, Universitas Andalas (91/UN/16.2/KEP-FK/2024). Written informed consent was obtained from all participants before their inclusion in the study.

Study design and population: This observational analytic study employed a cross-sectional design. The study population consisted of medical students from the Faculty of Medicine, Universitas Andalas, aged over 18 years. The study was conducted between November, 2023 and April, 2024. Participants were recruited using a consecutive sampling technique. A total of 113 individuals were screened and 102 subjects met the eligibility criteria for preliminary analysis. The final analysis focused on a sub-population of 51 subjects with a family history of T2DM.

Inclusion and exclusion criteria: Inclusion criteria:

- Provided informed consent
- Normal fasting blood glucose level (<100 mg/dL)

Exclusion criteria:

- History of diabetes mellitus
- Malignancy
- Heart, liver, kidney, or thyroid disease
- Current use of lipid-lowering therapy
- Pregnancy or breastfeeding

Data and sample collection: Each subject fasted for 10 hrs before venous blood sampling. Family medical history covering T2DM in first-degree relatives (father, mother, siblings) and the wider family (grandparents) was obtained via a questionnaire. Weight and height were measured to calculate Body Mass Index (BMI). Venous blood was analyzed for fasting glucose, triglycerides (TG), High-Density Lipoprotein Cholesterol (HDL-C) and fasting insulin.

Laboratory analysis:

- **Fasting blood glucose:** Hexokinase method
- **Triglycerides (TG):** Glycerol-3-phosphate oxidase (GPO) enzymatic colorimetric method
- **HDL-C:** Enzymatic colorimetric method
- **Insulin:** Electrochemiluminescence Immunoassay (ECLIA)

Glucose, TG and HDL-C analyses were conducted at the Central Laboratory of Universitas Andalas Hospital, while insulin analysis was performed at the Central Laboratory of Dr. M. Djamil Padang Hospital.

Index calculations: Fasting blood glucose was measured using the hexokinase method[8]. Triglyceride (TG) levels were determined using the glycerol-3-phosphate-oxidase (GPO) method, which is based on an enzymatic colorimetric principle. An enzymatic colorimetric method was also employed to measure HDL-C levels, while the Electrochemiluminescence Immunoassay (ECLIA) was used for insulin measurement. The following formulas were used for calculations:

$$\text{MetS} - \text{IR} = \frac{\text{Ln}\,(2 \times \text{Fasting glucose} + \text{Triglycerides}) \times \text{BMI}}{\text{Ln}\,(\text{HDL} - \text{C})}$$

$$\text{HOMA} - \text{IR} = \frac{\text{Fasting blood glucose (mg/dL)} \times \text{Fasting insulin (}\mu\text{U/mL)}}{405}$$

Statistical analysis: Agreement between MetS-IR and HOMA-IR in subjects with a family history (n = 51) and those with a first-degree family history (n = 36) was evaluated using the Kappa test[9]. Agreement strength was interpreted as:

- **Fair:** 0.21-0.40
- **Moderate:** 0.41-0.60
- **Substantial:** 0.61-0.80

A p-value <0.05 was considered statistically significant. Based on the ROC curve analysis, the MetS-IR index demonstrated an AUC of 0.662 (p = 0.005) for detecting insulin resistance using HOMA-IR as the reference. The optimal cut-off value determined using the Youden index was 32.83, yielding a sensitivity of 68.82% and a specificity of 63.80%. These findings indicate that MetS-IR has moderate discriminatory ability in identifying insulin resistance in this young adult population.

RESULTS AND DISCUSSION

This study has 51 non-diabetic adults with a family history of DMT2 as subjects. The characteristics of the subjects are shown in Table 1.

The majority of the study participants were female (62.74%), with nearly twice as many females as males. Almost one-third of the subjects were classified as obese (29.41%). Among participants with a family history of type 2 diabetes mellitus, more than two-thirds (70.59%) had a history of DMT2 in first-degree relatives (parents or siblings).

Table 2 shows that the median values for fasting blood glucose, fasting insulin, triglyceride and HDL-C levels in the study subjects were within the normal range.

The median fasting blood glucose level was 90 mg/dL (IQR:10), indicating normal glycemic status. The median fasting insulin level was 10.31 µU/mL (IQR: 6.81), suggesting relatively preserved insulin secretion. Median triglyceride levels were 80 mg/dL (IQR: 34), reflecting the absence of marked hypertriglyceridemia. Although the median HDL-C was 48 mg/dL (IQR: 14.5) and fell within the acceptable range, it remained below the optimal protective threshold, particularly among female participants, potentially indicating early cardiometabolic risk.

A relatively wide variability was observed across all parameters, which may reflect the presence of subgroups with higher metabolic risk, although overall, the subjects appeared to fall within normal ranges. The results of the agreement test of MetS-IR with HOMA-IR can be seen in Table 3.

In the sub-population with a family history of T2DM, the analysis showed a statistically significant, moderate agreement between MetS-IR and HOMA-IR, with a Kappa value of 0.490 (p = 0.001).

The results of the agreement test of MetS-IR with HOMA-IR in non-diabetic young adults with a history of T2DM in first-degree family can be seen in Table 4. Analysis of the sub-population with a first-degree family history of DM revealed a statistically significant agreement between MetS-IR and HOMA-IR, with a Kappa value of 0.649 (p = 0.001).

A higher Kappa value was observed when the analysis was performed on the sub-population with a first-degree family history of DM. This indicates that MetS-IR could be a more effective screening tool for insulin resistance in specific populations, particularly those with a genetic predisposition.

No study has specifically examined the relationship between MetS-IR and HOMA-IR in healthy individuals with a first-degree family history of diabetes. However, previous research consistently indicates that a family history of diabetes, particularly among first-degree relatives, is associated with elevated HOMA-IR levels[9-12]. Several studies have reported that individuals with a familial history of type 2 diabetes exhibit higher HOMA-IR values compared with those without such a history[13]. For example, Ahmed found that non-diabetic individuals with first-degree relatives affected by diabetes had HOMA-IR values that were 87.5% higher than those of individuals without a family history of diabetes[14].

Table 1: Characteristic of subjects

Variables	Frequency (%)	Median (IQR)
Age (years old)		20 y. o. (2)
Gender		
Male	19 (37.26)	
Female	32 (62.74)	
BMI (kg/m²)		
Obeses (≥25)	15 (29.41)	
Not Obese (<25)	36 (70.59)	
History of DMT2 in the first-degree family		
Yes	36 (70.59)	
No	15 (29.41)	

Table 2: Median of blood glucose, fasting insulin, triglyceride and HDL-C levels of subjects

Variables	Median (IQR)
Fasting blood glucose (mg/dL)	90 (10)
Fasting insulin (μU/mL)	10.31 (6.81)
Triglycerides (mg/dL)	80 (34)
HDL-C (mg/dL)	48 (14.5)

Table 3: Agreement test of MetS-IR with HOMA-IR in non-diabetic young adults with T2DM family history

	HOMA-IR						
	Not insulin resistance (< 2.2)		Insulin resistance (≥2.2)				
Variable	N	%	N	%	Total	Kappa value	p-value
MetS-IR							
Not insulin resistance (<32.83)	18	35.29	7	13.73	25	0.490	0.001
Insulin resistance (≥32.83)	6	11.76	20	39.22	26		
Total	24		27		51		

Table 4: Agreement test of MetS-IR with HOMA-IR in non-diabetic young adults with a history of T2DM in first-degree family

	HOMA-IR						
	Not Insulin resistance (< 2.2)		Insulin resistance (≥ 2.2)				
Variable	N	%	n	%	Total	Kappa value	p-value
MetS-IR							
Not Insulin Resistance (< 32.83)	11	30.56	3	8.33	14	0.649	0.001
Insulin Resistance (≥32.83)	3	8.33	19	52.78	22		
Total	14		22		36		

The offspring of individuals with T2DM are considered a high-risk group for developing the disease, as this pathological condition can be inherited. Individuals with parents who have type 2 diabetes possess a two to four times greater relative risk of developing the disease themselves[1]. In a 2018 study, Aman *et al.*[4] investigated 64 subjects with a first-degree family history of T2DM found that 51.6% exhibited insulin resistance. That study further revealed that young adults with a parental history of T2DM had up to a 10.3-fold higher risk of having insulin resistance compared to individuals without such a history[5].

Insulin resistance is a primary component in the pathophysiology of T2DM. It is closely associated with obesity, elevated serum triglyceride levels and decreased HDL cholesterol levels[1,5]. These three parameters are precisely the components measured by the MetS-IR index, which may explain why a higher agreement was found in the sub-populations with a family and first-degree family history of DM compared to subjects without such a history.

The Kappa value in this study was highest in the analysis of the sub-population with a first-degree family history of T2DM. However, despite this finding, MetS-IR cannot yet replace HOMA-IR for detecting insulin resistance in any of the populations or sub-populations analyzed in this study, because an adequate agreement is defined as a Kappa value of 0.8 or higher.

This study has several limitations. First, the subjects were volunteers selected from a specific population of medical students who met certain criteria, which introduces a potential for selection bias and the sample may not fully represent the

general non-diabetic adult population. Second, the generalizability of the findings is restricted due to the very narrow age range of the subjects, which was between 18 and 22 years old. Finally, this research did not employ the gold-standard hyperinsulinemic-euglycemic clamp (HEC) for a definitive diagnosis of insulin resistance; instead, it relied on HOMA-IR as a surrogate marker for comparison.

CONCLUSION

The level of agreement between MetS-IR and HOMA-IR in detecting insulin resistance increased from moderate (Kappa = 0.490) to substantial (Kappa = 0.649) in subjects with a family and first-degree family history of T2DM, respectively. Although MetS-IR showed better potential in this genetically at-risk group, its agreement value did not reach the threshold considered adequate to replace the reference method. Therefore, it can be concluded that the MetS-IR index cannot yet substitute HOMA-IR as a tool for detecting insulin resistance. For future research, it is recommended to use the gold-standard HEC method to more definitively classify subjects with insulin resistance. Furthermore, balancing the number of subjects based on gender, a broader age range and T2DM family history status is also advised to reduce bias and enable a more in-depth comparative analysis between groups.

SIGNIFICANCE STATEMENT

This study discovered that MetS-IR demonstrates moderate to substantial agreement with HOMA-IR in non-diabetic adults with a family history of T2DM, particularly in those with a first-degree family history, which can be beneficial for early identification of insulin resistance in at-risk populations. This study will help researchers uncover the critical areas of metabolic assessment and non-invasive screening methods that many researchers were not able to explore. Thus, a new theory on rapid and cost-effective detection of insulin resistance may be arrived at.

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