




# Unveiling the Significance of Surrogate Markers of Insulin Resistance in Metabolic Health Assessment

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## ABSTRACT

Recent years have evidenced an alarming increase in the incidence of diabetes mellitus (DM) and other metabolic disorders. Rapid urbanization and lifestyle changes have been the major factors for this increase. Early diagnosis is the key to better risk stratification and prompt management of these patients. Insulin resistance (IR) plays a pivotal role in the pathogenesis of various metabolic disorders. Assessing the IR in the initial stages would therefore help in early detection of patients who are susceptible to metabolic disorders. The hyperinsulinemic-euglycemic clamp technique has been the gold standard method for assessing IR. The major limitation of this technique is it is invasive and requires a specialized setup. Hence, identifying reliable surrogate markers for assessing IR is the need of the hour both in clinical and research settings. This review delves into the current knowledge of surrogate markers utilized to assess IR, providing a comprehensive overview of their strengths, limitations, and emerging trends. We explore commonly employed surrogate markers such as fasting insulin, homeostatic model assessment-insulin resistance (HOMA-IR), adiponectin, triglyceride-to-glucose index, etc. The search for accurate and cost-effective surrogate markers holds significant promise for early detection, risk stratification, and targeted interventions. This review aims to contribute to the existing knowledge on IR and highlight future directions in the quest for effective markers for IR.

**Keywords:** Adiponectin, Homeostatic model assessment-insulin resistance, Insulin resistance, Metabolic health assessment, Surrogate markers, Triglycerides and glucose index.

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## INTRODUCTION

Insulin resistance (IR) is described as a decline in the rate of glucose elimination in humans in response to particular insulin concentrations. It is a medical condition characterized by reduced effectiveness of insulin on the tissues and is linked to metabolic disorders like hyperglycemia along with hypertriglyceridemia. Insulin resistance can emerge from decreased responsiveness of the active organs and tissues to insulin.<sup>1</sup> Adipocytes in IR secrete free fatty acids that are absorbed by the liver and converted into very low density lipoprotein (VLDL) cholesterol rich in triglycerides (TG). This VLDL interacts with low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol to exchange lipids. Due to high triglyceride content, the HDL is eliminated rapidly by the kidneys it is unable to engage in reverse cholesterol transport. Both IR and hyperglycemia lead to endothelial dysfunction, proliferation of vascular smooth muscle, and inflammation in their respective ways.<sup>2</sup>

Assessing IR would be beneficial in identifying individuals at an elevated risk of complications associated with diabetes and MS. There are various methods to assess IR. The hyperglycemic clamp method is the major standard technique for measuring the quantity of glucose the body metabolizes after a controlled hyperglycemic shock and measuring beta-cell sensitivity to glucose.<sup>3</sup> The major disadvantage of this method is an invasive technique. Several other noninvasive techniques such as homeostatic model assessment-insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), triglycerides and glucose (TyG) index, etc., are being used as alternative markers of the euglycemic clamp technique. In apparently healthy subjects, Luis E. Simental-Mendía et al., showed, TyG index had high sensitivity and low specificity for diagnosing

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insulin resistance, in comparison with HOMA-IR.<sup>4</sup> Therefore, the TyG index has been suggested as an alternative indicator of IR, and it has been demonstrated to correlate with other approaches used to evaluate IR, such as HOMA-IR and the hyperinsulinemic-euglycemic clamp (HEC).<sup>2,5,6</sup>

Earlier studies have tried to highlight the importance of various surrogate markers of IR. However (Reviewers studies), this review provides a comprehensive overview of IR, its pathophysiology, and associated disorders and further provides insights into the various techniques used for assessing IR, their clinical utility, and limitations. The review specifically focuses on those methods that are simple, and easily adaptable in clinical setups with limited facilities; and also provides insights into future directions in the quest for effective markers for IR.

## PATHOGENESIS

Insulin resistance is a condition characterized by a reduced responsiveness of the body's cells to the hormone insulin, produced by the pancreas. Insulin plays a vital role in controlling blood glucose levels by enabling the cells to take up glucose from the bloodstream, where it can be utilized for energy or stored. In individuals experiencing IR, cells fail to respond to insulin, resulting in elevated blood glucose levels.<sup>7</sup>

In instances of IR, adipocytes release free fatty acids that the liver incorporates into triglyceride-rich, VLDL. This VLDL engages in lipid exchange with LDL and HDL. Notably, triglyceride-rich HDL is swiftly eliminated by the kidneys, rendering them unable to contribute to reverse cholesterol transport. Insulin resistance and hyperglycemia operate independently to foster endothelial dysfunction, vascular smooth muscle proliferation, and inflammation in skeletal muscle. In the context of IR, there is a diminished response to circulating insulin, leading to a decrease in glucose transport and a reduction in muscle glycogen synthesis. Insulin resistance in skeletal muscle stems from a deficiency in glucose transport, characterized by reduced translocation, fusion, or exposure and activation of GLUT-4 glucose transporters. The irregularities in GLUT-4 translocation within muscle seem to arise from deficiencies in intracellular signaling. These deficiencies may either be inherent in the tissue or attributed to circulating or paracrine factors, such as hyperglycemia (glucose toxicity), heightened serum levels of free fatty acids, or increased TNF- $\alpha$ . Furthermore, insulin-stimulated glucose uptake in adipocytes is also impaired, primarily due to the down-regulation of GLUT-4 expression.<sup>8-10</sup>

In the liver, IR is selective because it continues to stimulate the production of fatty acids while failing to stop gluconeogenesis. In adipose tissue, IR is characterized by compromised insulin-stimulated glucose transport and diminished inhibition of lipolysis.<sup>11</sup> Insulin resistance plays a significant role in the development of obesity, diabetes, and IR syndrome, and is linked to an elevated risk of cardiovascular diseases.<sup>12</sup>

## Diseases Associated with IR

### *Metabolic Syndrome (MS)*

Insulin resistance is a major feature of MS, a condition characterized by a combination of abdominal obesity, elevated blood pressure, increased blood sugar levels, elevated triglyceride levels, and reduced levels of HDL cholesterol. Insulin resistance and MS are linked in both ways. Insulin resistance might lead to the development of MS by impairing cells' capacity to react to the effects of insulin, which can cause high blood sugar levels (Hyperglycemia), increased fat storage, and other metabolic abnormalities. On the other side, IR can be made worse by the MS elements, such as obesity and high blood sugar.<sup>13,14</sup>

### **Cardiovascular Disease**

Insulin resistance is associated with a high risk of disease of the heart, like myocardial infarction, and stroke. It contributes to the development of atherosclerosis (hardening and narrowing of the arteries) and inflammation. Insulin resistance is related to endothelial dysfunction, because of which the blood vessel lining cells lose their function. When the endothelium fails to function effectively, it can lead to atherosclerosis, a condition in which fatty deposits (plaques) accumulate in the arteries. The plaques formed can constrict also stiffen arteries, limiting the flow of blood and increasing the danger of heart attacks as well as strokes.<sup>15</sup>

Insulin resistance can result in increased sympathetic nervous system activity and sodium retention, both of which contribute to hypertension. Because it puts pressure on the blood vessels and heart, hypertension stands as a significant factor for CVD.<sup>15</sup>

## Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome is an endocrine disease impacting females and is marked by IR, irregular menstrual cycles, excess hair growth, and ovarian cysts. Elevated insulin levels can stimulate the ovaries to create more androgens (male hormones) such as testosterone. This can result in PCOS symptoms such as hirsutism (excess hair growth), acne, and irregular menstrual cycles. Insulin resistance can interfere with the normal hormonal regulation of the menstrual cycle, resulting in irregular or missing ovulation. According to Evanthia Diamanti-Kandarakis and Dunaif the link between PCOS and IR has unveiled the significance of insulin as a crucial reproductive hormone emphasizing the critical functioning of insulin signaling in the CNS for the process of ovulation.<sup>16</sup> Park KH et al. concluded that PCOS women have significant IR which is independent of adiposity.<sup>17</sup>

## Non-alcoholic Fatty Liver Disease (NAFLD)

The fat accumulated in the liver is closely connected to IR, which can lead to NAFLD, a condition that ranges from simple fatty liver to more severe forms of liver damage.<sup>18</sup> A study by Matthew J et al. describes the NAFLD-induced alteration in the secretion of liver proteins, lipids, other metabolites, and miRNAs. These molecules in turn impact the metabolism of the liver, muscle, adipose tissue, and pancreas ultimately resulting in IR.<sup>19</sup>

## Assessment of IR

A marker is a quantifiable characteristic identified in a biological sample that is easily available or discovered by imaging of tissue, which can represent the pathophysiology of the substantial disease, anticipate further occurrences, and also demonstrate the efficacy of treatment. They function as sensitive indicators for the detection of initial signs of damage to target organs.<sup>20</sup> Verified risk-evaluation techniques are currently unable to adequately take into consideration the elevated risk factors linked to MS. Therefore, it is necessary to identify the syndrome's markers.<sup>21</sup>

Numerous human studies are underway to develop methods for estimating IR. It is crucial to establish suitable animal models for investigating the epidemiology, pathophysiological causes, outcomes of therapeutic interventions, and medical advancements related to individuals with IR. Insulin resistance serves as a recognized independent indicator for various diseases. Even before the onset of disease symptoms, IR is already present. Identifying and promptly managing individuals with IR is essential, as hyperinsulinemia may persist unnoticed for an extended period, increasing the risk of developing other components of the syndrome and associated disorders.<sup>22,23</sup>

Consequently, there is a need for a dependable method to rapidly assess insulin sensitivity and monitor changes resulting from therapeutic interventions.

## Gold Standard Method for Assessment of IR

### *Hyperinsulinemic Euglycemic Clamp (HEC)*

The HEC is regarded as the gold standard test for evaluating sensitivity to insulin and assessing IR. It is a sophisticated and precise technique used in research settings and specialized clinical centers. The principle of HEC involves the continuous infusion of

insulin into the bloodstream to mimic the body's natural insulin secretion, combined with simultaneous adjustments of glucose infusion to maintain a stable blood glucose level (euglycemia). The infusion rate of glucose required to sustain stable blood sugar levels indicates the body's sensitivity to insulin.<sup>24</sup> During the HEC, glucose and insulin levels are monitored frequently. By varying the insulin infusion rate and monitoring the corresponding rate of glucose infusion required to keep up euglycemia, researchers can calculate the "glucose disposal rate" (GDR), which is a direct measure of insulin sensitivity. A higher GDR indicates better insulin sensitivity, while a lower GDR suggests IR.<sup>3,25</sup>

A study conducted by Charmaine S et al. established an endpoint for defining IR using HEC. The researchers also presented a classification system to predict IR based on regularly assessed biochemical and clinical markers.<sup>26</sup> Ralph A et al. study concluded that the hyperglycemic clamp technique serves as a highly reproducible method for measuring the quantity of glucose metabolized by the body in response to a regulated hyperglycemic stimulus. This approach is also effective in evaluating beta-cell sensitivity to glucose.<sup>3</sup>

The HEC provides a direct assessment of insulin sensitivity, making it a reliable method for comparing IR among different individuals or study groups. It allows for precise measurements and can detect subtle changes in insulin sensitivity.<sup>27</sup> Despite its accuracy, the HEC is a complex and labor-intensive procedure that requires skilled personnel and specialized equipment. As a result, it is not a practical test for routine clinical use or large-scale screenings. Additionally, it can be uncomfortable for the participant due to the continuous blood sampling and insulin infusion.<sup>3</sup> While the HEC is an excellent tool for research purposes, it may not be feasible or necessary for routine clinical practice. Instead, more straightforward approaches such as Fasting insulin and glucose levels, oral glucose tolerance tests, as well as surrogate markers (e.g., HOMA-IR) are frequently employed in clinical settings.

### Need for Surrogate Markers

Surrogate markers are widely utilized in both medical research and clinical practice they ultimately measure a specific condition when direct measurement might be impossible, invasive, or costly. In the context of testing IR, surrogate markers serve as suitable and informative tools to assess the condition without the need for complex or painful procedures. To measure insulin sensitivity, surrogate markers for IR offer a quicker and easier method. Although the surrogate markers provide a practical method to calculate IR, it's crucial to be aware of their limitations. Rather than offering a precise measurement, they offer an approximation of the situation. Additionally, the precision of these indicators may be impacted by individual variation, hereditary variables, and other health issues.

### Surrogate Markers

#### *Adiponectin Levels in IR*

Adiponectin is a hormone that is primarily produced and secreted by adipose tissue, which is the body's fat cells. It has a significant function in regulating several metabolic functions in the body, including glucose regulation and fatty acid breakdown. They enhance insulin sensitivity, meaning they help cells respond better to insulin and improve glucose utilization. Adiponectins also stimulate fatty acid oxidation (fat burning) and inhibit the production of glucose in the liver.<sup>12</sup>

#### *Adiponectin and IR*

Numerous researchers have established the inverse connection between adiponectin levels as well as IR. In conditions where adiponectin levels are low, as seen in obesity and type 2 diabetes mellitus (DM), insulin sensitivity is impaired. Adiponectin can be used as a biomarker for IR. Adiponectin levels can be measured in blood samples to identify individuals at risk of or already experiencing IR. Low adiponectin levels suggest a higher likelihood of IR. Adiponectin level scans also help assess the severity and progression of IR. Lower adiponectin levels are associated with a higher possibility of developing disturbances associated with IR, such as type 2 DM, CVS disorders, as well as MS. It's important to note that while adiponectin is a valuable biomarker, it is not the only factor to consider in assessing IR. Other biomarkers, such as fasting insulin levels, glucose tolerance tests, and HbA1c (glycated hemoglobin) levels, are often used in conjunction with adiponectin to provide a comprehensive evaluation of IR.<sup>28</sup> Given the positive impact of adiponectin on insulin sensitivity and glucose metabolism, it has been considered a potential therapeutic target for IR and linked to conditions like type 2 diabetes and MS.<sup>29</sup> However, direct administration of adiponectin as a therapeutic agent has been challenging due to its large size and the complexities associated with its production and stability. Alternative therapeutic approaches include lifestyle modifications such as regular physical activity and a balanced diet can increase adiponectin levels. Weight loss and regular exercise have been shown to raise adiponectin levels, leading to improved insulin sensitivity. Some medications used to treat diabetes, such as thiazolidinediones (TZDs), have been found to increase adiponectin levels. Thiazolidinediones improve insulin sensitivity and glycemic control partly through their effect on adiponectin. Certain dietary supplements and nutraceuticals, like omega-3 fatty acids and certain polyphenols, have been associated with increased adiponectin levels, potentially improving insulin sensitivity. Adiponectin therefore may be the molecular link between obesity and IR, and it may also act as a biomarker for the MS, according to research by Buechler et al. Schöndorf et al. in their research, proposed a close association between adiponectin concentrations and IR, along with components of the MS, in individuals with type 2 DM. He also emphasized that the concentration of adiponectin proves valuable in addition to the criteria employed for identifying obese individuals having MS.<sup>30</sup>

#### *Homeostatic Model Assessment of IR*

Homeostatic model assessment IR is a broadly used surrogate indicator for IR. Matthews et al. first proposed it in 1985 as a technique for assessing insulin sensitivity and IR based on fasting glucose values and insulin levels. Because of its simplicity, cost-effectiveness, and non-invasiveness, it has now become a popular tool in both clinical and research contexts.<sup>27</sup> The HOMA-IR is calculated using a simple formula  $\text{Fasting Insulin } (\mu\text{U/mL}) \times \text{Fasting Glucose } (\text{mmol/L}) / 22.5$ . An increased HOMA-IR indicates decreased Insulin sensitivity and increased IR. A study by Hui-Qi Qu et al. concluded increased sensitivity and specificity of HOMA-IR >3.80 for IR.<sup>31</sup> Dicky Levenus Tahapary et al. concluded that the HOMA-IR is a simple and frequently used method for determining IR.<sup>32</sup>

#### *Clinical Use and Applications*

- **Screening for IR:** Homeostatic model assessment IR is preferred as a preliminary screening tool to recognize individuals at risk of IR or type 2 DM.



- **Research Studies:** Homeostatic model assessment IR is widely employed in large-scale epidemiological studies and clinical trials to evaluate insulin sensitivity and resistance within the study populations.
- **Predicting Outcomes:** Homeostatic model assessment IR has been linked with various physical outcomes, as well as the risk of CVS diseases as well as metabolic disorders.

### Limitations

Homeostatic model assessment IR provides an estimate of IR and sensitivity, but it is not a direct measurement like the HEC, which is accepted as the gold standard.

#### Insulin Clearance

Homeostatic model assessment IR does not account for variations in insulin clearance rates, which may vary among individuals. Homeostatic model assessment IR relies on fasting blood samples, which may not fully represent the dynamic insulin response to glucose challenges.

#### Variability

Factors such as age, body weight, ethnicity, and medication use can influence the accuracy of HOMA-IR.<sup>33</sup>

### Fasting Insulin, Fasting Glucose and Fasting C-peptide Levels

Evaluation of fasting insulin levels plays a pivotal role in assessing IR.<sup>34</sup> In insulin-resistant subjects, cells do not react competently to glucose as well as insulin uptake is impaired. As a result, the pancreas releases more insulin to overcome this resistance and maintain glucose homeostasis. This results in higher fasting insulin levels as the pancreas is constantly producing and secreting more insulin even during fasting periods.<sup>35</sup> Laakso M concluded that, particularly in people with unusual glucose tolerance, only the fasting insulin level should be utilized as a marker of IR.<sup>36</sup> Elevated fasting insulin levels are directly linked to an increase in resistance to insulin-mediated glucose uptake. Notably, these changes can occur even when there are no identifiable causes for reduced insulin responsiveness. According to Olefsky J et al. the observed increase in fasting insulin levels appears to be an alternate mechanism, aimed at overcoming the resistance to glucose uptake.<sup>37</sup>

While fasting insulin levels are a valuable marker, they also have some limitations:<sup>38</sup>

- **Heterogeneity:** Insulin resistance is a unique condition with various contributing factors, and the correlation between fasting insulin levels and IR may not be the same in all individuals.
- **Other Factors:** Fasting insulin levels can be affected by factors such as obesity, physical activity, and genetics.
- **Different Reference Ranges:** There is no universally agreed-upon cutoff for fasting insulin levels indicative of IR. Reference ranges may vary among laboratories and populations.

### Fasting Glucose Levels

Fasting glucose levels are an essential indicator in assessing IR. Elevated fasting glucose levels are a characteristic feature of pre-diabetes, a condition in which blood glucose levels are higher than normal but not yet at the threshold for a diabetes diagnosis. Pre-diabetes poses a substantial risk factor for the onset of type 2 DM. Impaired fasting glucose is a component of MS, a cluster of metabolic abnormalities that collectively raise the risk of developing

type 2 DM and Cardiovascular disorders disorders.<sup>39</sup> Nobuo Sasaki et al. found that in the initial phases of impaired insulin metabolism, hyperglycemia, and hyperinsulinemia play substantial roles in contributing to the development of hypertension.<sup>35</sup>

### Limitations

#### Heterogeneity

Insulin resistance is a complex condition with various contributing factors, and the correlation between fasting glucose levels and IR may not be the same in all individuals. Fasting glucose levels can be affected by factors such as diet, physical activity, medications, and stress.

### Fasting C-peptide

Fasting C-peptide levels are often used in clinical practice as part of the assessment for IR and other related conditions. The C-levels of fasting C-peptide are utilized to assess the basal insulin secretion of the body, which is the amount of insulin released by the pancreas in the fasting state. In conditions like IR and type 2 DM, the pancreas increases insulin secretion often to balance reduced insulin sensitivity. Therefore, measuring C-peptide levels can give insights into the pancreas' ability to produce insulin. When assessing insulin levels in the blood, C-peptide is preferred over insulin itself because it helps distinguish endogenous (produced by the body) insulin from exogenous insulin (administered externally, e.g., in insulin injections). This differentiation is crucial in cases where patients are on insulin therapy.<sup>40,41</sup> The extended half-life of C-peptide, roughly 5-fold longer than insulin, further supports its use as a biomarker with lower susceptibility to fluctuations.<sup>40</sup>

### The Quantitative Insulin Sensitivity Check Index

The QUICKI is a simple as well as convenient method used to estimate the sensitivity of insulin in both research and clinical settings. It is calculated from fasting levels of glucose and insulin and offers a rapid assessment of insulin sensitivity. Here is a review of QUICKI in the context of IR. The QUICKI is derived using the formula:  $QUICKI = 1/(\log \text{fasting insulin } \mu\text{U/mL} + \log \text{fasting glucose mg/dL})$ . It is based on the contrary relationship between insulin sensitivity as well as fasting insulin levels.<sup>42</sup> Higher QUICKI values indicate better insulin sensitivity, whereas lower QUICKI values suggest decreased insulin sensitivity and a higher likelihood of IR. The main advantage of QUICKI is its simplicity and ease of use. It only requires measurements of fasting glucose and fasting insulin, which are standard tests commonly available in clinical laboratories. Quantitative insulin sensitivity check index has been shown to correlate reasonably well with more complex and invasive techniques for measuring insulin sensitivity, such as the HEC. Quantitative insulin sensitivity check index is a consistent surrogate marker for IR in large-scale studies as well as clinical research where more labor-intensive tests may not be feasible.<sup>43</sup> Chen, Hui et al. concluded that QUICKI is a straightforward as well as robust marker of insulin sensitivity. It proves to be valuable for assessing and monitoring IR in hypertensive patients in both clinical practice and research studies, particularly in the context of IR, DM, and glucose clamp studies.<sup>42</sup>

### Limitations

It provides only estimation and may not capture all aspects of IR. Moreover, QUICKI may not be as accurate in certain populations,

such as subjects who have extreme IR or those with type 1 DM.<sup>39</sup> Quantitative insulin sensitivity check index may not detect dynamic changes in insulin sensitivity, such as postprandial variations. It is more representative of fasting insulin sensitivity.<sup>43</sup>

### Triglycerides and Glucose Index

The TyG index, derived from the fasting levels of glucose and triglycerides, has been proposed as an alternate marker for IR. This index, which involves measurements of fasting triglyceride and plasma glucose, has demonstrated correlations with other established markers of IR, including HOMA-IR and the HEC, as well as associations with MS.<sup>2,5,6</sup> Triglycerides and glucose index is the product of serum TG and fasting serum glucose levels. The TyG index is a relatively new marker used as a surrogate measure of IR. Formula: TyG index =  $\text{Ln} [\text{fasting triglycerides (mg/dL)} \times \text{fasting glucose (mg/dL)/2}]$ .<sup>8</sup> Triglycerides and glucose index is based on the observation that both high triglyceride levels and high glucose levels are associated with IR. Therefore, combining these two factors into a single index can help in identifying individuals at risk for metabolic disorders. The TyG index is a useful tool for predicting IR, type 2 DM, and other CVS risk factors.<sup>44</sup> Subjects with IR may be detected using lipid-based insulin action markers. In people with IR, increased triglycerides, and hypoalphalipoproteinemia are symptoms of dyslipidemia.<sup>8</sup> Elevated triglyceride (TG) levels have been found to interrupt with metabolism of glucose in all muscles. This observation aligns with the literature that the increase in triglycerides in both tissues and serum is associated with reduced insulin sensitivity.<sup>45</sup> A study conducted by Fernando Guerrero-Romero et al. concluded that the triglyceride-glucose index is highly sensitive and specific for the recognition of patients with lowered insulin sensitivity.<sup>46</sup> Another study was done by Adriana Sanchez-García et al. on nondiabetic healthy individuals to establish the diagnostic accuracy of the TG index in assessing IR. This study demonstrated low to moderate evidence of the TG index as an alternate marker for IR.<sup>47</sup>

### Lipid Indices as Surrogate Markers of Insulin Resistance

Lipid indices such as lipid accumulation product (LAP), visceral adiposity index (VAI), and triglyceride to TG/HDL ratio are indeed used as surrogate markers of IR.

- **Lipid Accumulation Product (LAP):** Lipid accumulation product is calculated using waist circumference and fasting triglyceride levels. It's considered a marker of lipid over-accumulation in non-adipose tissues. Studies have shown LAP to be associated with IR, MS, and cardiovascular risk. Higher LAP values are indicative of higher cardiometabolic risk.  $\text{LAP} = (\text{waist circumference in cm} - 65) \times (\text{triglycerides in mmol/L})$ .
- **Visceral Adiposity Index (VAI):** Visceral adiposity index is a mathematical model based on anthropometric (waist circumference, BMI) and metabolic (triglycerides, HDL cholesterol) parameters. It aims to quantify visceral adiposity and its metabolic implications. It's calculated using the formula derived from gender-specific equations. Elevated VAI is correlated with IR, MS, and cardiovascular risk.
- **TG/HDL Ratio:** The ratio of triglycerides to HDL cholesterol is a simple and commonly used marker. Higher values are associated with IR and atherogenic dyslipidemia. It reflects both lipid and glucose metabolism. A ratio above 3.5 is considered indicative of IR and increased cardiovascular risk. These markers

are useful because they offer insights into metabolic health beyond traditional measures like BMI or waist circumference alone. However, they are considered surrogate markers and are typically used alongside other clinical assessments for a comprehensive evaluation of metabolic health and IR. Insulin plays a role in regulating triglyceride metabolism, and resistance to its action can lead to increased production and reduced clearance of triglycerides from the bloodstream.<sup>48,49</sup>

Studies have investigated the effectiveness of novel lipid indices in identifying IR. Lipid accumulation product showed higher accuracy than the TyG index and VAI. Further combining BMI and waist circumference with TyG index further improved accuracy, surpassing LAP. Although the exact mechanism of lipid indices in causing IR is unclear, glucolipotoxicity has been implicated as one of the mechanisms. Visceral adiposity index and LAP correlated inversely with insulin sensitivity. Compound indices like TyG-BMI and TyG-WC, combining the TyG index with obesity parameters, showed promising results in identifying IR, particularly in diverse populations. Lipid accumulation product index was also identified as a more reliable discriminator of IR as compared with VAI, TyG, and TG/HDL-C ratio indexes.<sup>48-50</sup>

### Advantages

These indices are based on inexpensive measurements such as waist circumference and triglycerides, and are also accessible in underdeveloped countries, and rural setups with limited facilities.

### Limitations

Most of these studies were cross-sectional studies. In many of these studies, comparison was not done with the gold standard technique. Studies were conducted in different ethnic groups, and need to be validated in other ethnic groups for their widespread applicability.<sup>49</sup>

### Future Directions in the Quest for Effective Markers of Insulin Resistance

Researchers are exploring various avenues to improve the detection and management of IR. Instead of relying on single markers, researchers are exploring the development of biomarker panels that combine multiple markers from different biological pathways associated with IR. These panels may enhance diagnostic accuracy and predictive power.

### Genetic Markers

Advancements in genomics have revolutionized the identification of genetic variants linked to IR, offering valuable insights into its underlying mechanisms and potential therapeutic targets. By analyzing these variants, researchers attempt to establish genetic markers capable of more accurately predicting an individual's risk of IR. Notable genetic markers under study include variants in genes such as TCF7L2, PPARG, ADIPOQ, IRS1, and the Glucokinase gene, all implicated in regulating insulin sensitivity, adipocyte differentiation, glucose sensing, and insulin secretion.<sup>51</sup>

In recent investigations, genome-wide association studies (GWAS) have shown 369 SNP loci linked to TG: High-density lipoprotein-cholesterol (HDL-C) ratios, shedding light on adipocyte biology, endocrine functions, growth and cancer pathways, hepatic genes, and female reproductive system components. Additionally, studies have identified potential genetic markers of IR and atherosclerosis in type 2 DM patients with coronary artery

disease (CAD), including CH13L1, CD36, LEPR, RETN, IL-18, RBP-4, and RARRES2 genes.<sup>51,52</sup>

Technological approaches such as CRISPR, 3C, and eQTL are employed to explore structural and functional associations between genetic loci revealed by GWAS or exome sequencing and regional or distal genes. CRISPR, particularly as an in vitro screening platform, holds promise in pinpointing causal genes at loci associated with MS and IR.<sup>53</sup>

Investigations into these genetic markers of IR, facilitate risk prediction and potentially inform personalized treatment strategies. However, it's crucial to recognize that IR is influenced by both genetic and environmental factors, likely involving the contribution of multiple genes to its development.

### Omics Technologies

Omics technologies, such as metabolomics, proteomics, and transcriptomics, offer a comprehensive view of biological molecules and pathways involved in IR. Integrating data from these omics approaches may lead to the discovery of novel biomarkers and therapeutic targets. Omics technologies have revolutionized the field of biomedical research, offering comprehensive insights into various aspects of health and disease, including IR.

#### Proteomics

Proteomics involves the large-scale study of proteins expressed in a cell, tissue, or organism. By identifying and quantifying proteins associated with IR, proteomics can uncover biomarkers for early detection, prognosis, and therapeutic targets.<sup>54</sup>

#### Metabolomics

Metabolomics analyzes the complete set of small molecules (metabolites) present in a biological sample. This approach enables the identification of metabolic signatures associated with insulin.<sup>55</sup>

#### Lipidomics

Lipidomics focuses on the comprehensive analysis of lipid species within a biological system. Since lipid metabolism plays a crucial role in IR and related metabolic disorders, lipidomics can provide insights into lipid profiles associated with IR and its complications.<sup>56</sup>

#### Glycomics

Glycomics studies the structure and function of carbohydrates (glycans) in biological systems. Abnormalities in glycan structures have been linked to IR and type 2 DM. Glycomics can uncover changes in glycan composition associated with IR and its complications.

By integrating data from these omics technologies, researchers can gain a holistic understanding of the molecular mechanisms underlying IR, leading to the development of more effective diagnostic tools and targeted therapies.

### Microbiome Analysis

Growing evidence suggests that the gut microbiome plays a role in regulating metabolism and insulin sensitivity. Scientists are exploring the composition of the gut microbiome and its metabolic by-products as potential indicators of IR.

In one study, variations in gut microbial  $\beta$  diversity were linked with IR, with higher  $\alpha$  diversity associated with lower IR. Additionally, analysis of a middle-aged population-based cohort, comprising black and white individuals, revealed notably lower

microbial diversity and reduced levels of butyrate-producing genera in those diabetic patients who were on treatment and those with longer diabetes duration compared to those with normal glucose levels.<sup>57</sup> Another study explored the connection between fecal carbohydrates and low-grade inflammation, underscoring the significance of investigating microbial metabolites in the pathogenesis of IR.<sup>58</sup>

### Advanced Imaging Techniques

Advanced imaging techniques for assessing IR involve sophisticated medical imaging modalities that allow for the visualization and quantification of specific anatomical or physiological parameters associated with IR.

#### Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging provides high-resolution images of tissues within the body and can be utilized to assess adipose tissue distribution, liver fat content, and muscle composition—all of which are linked to IR.

#### Computed Tomography (CT)

Computed tomography scanning can assess visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) volumes, as well as liver fat content, providing valuable information regarding IR and metabolic health.

#### Positron Emission Tomography (PET) Imaging

Positron emission tomography imaging with specific radiotracers can assess glucose metabolism in different tissues, allowing for the evaluation of insulin sensitivity.<sup>59,60</sup>

These advanced imaging techniques offer non-invasive or minimally invasive means to evaluate various aspects of IR, aiding in both research studies and clinical management of metabolic disorders. However, it's important to note that these techniques may not be widely available in all medical settings and can be expensive.

### Artificial Intelligence (AI)

Assessing IR using AI and machine learning algorithms has gained significant attention in recent years due to its potential to improve diagnostic accuracy and personalized treatment strategies for conditions like diabetes. Artificial intelligence algorithms can analyze large volumes of data from various sources including electronic health records, genetic data, lifestyle factors, and medical imaging to identify patterns associated with IR.<sup>61</sup>

Machine learning models can be trained on these datasets to predict the likelihood of IR in individuals based on their specific characteristics. Artificial intelligence algorithms can automatically identify which features or variables are most relevant for predicting IR, helping to streamline the diagnostic process. Artificial intelligence systems can provide decision support to healthcare professionals by interpreting complex data and assisting in the diagnosis and management of IR.<sup>62</sup>

By analyzing individual patient data, AI algorithms can provide treatment plans to the specific needs of each patient, optimizing outcomes and potentially reducing the risk of complications associated with IR.<sup>63</sup> However, it's essential to ensure that these algorithms are validated and integrated into clinical practice responsibly and ethically.

By combining insights from genetics, molecular biology, microbiology, imaging, and data analytics, researchers aim to

**Table 1:** Surrogate markers of insulin resistance

Method	Formula	Normal value	Advantage	Disadvantage
Hyperinsulinemic euglycemic clamp	HEC = MCR/I <sub>mean</sub> *	4–8 mg/min per kg body weight	Direct measure of insulin under steady state condition	Labor-intensive, expensive, time-consuming, intravenous insulin infusion, frequent blood sampling.
HOMA-IR	HOMA-IR = [Fasting Insulin (μU/mL) × Fasting Glucose (mmol/L)]/22.5	<1 is insulin sensitivity 1–2.9 suggestive of insulin resistance >2.9 significant of insulin resistance.	Simple, less invasive, predicts fasting steady-state–glucose and insulin levels	Insulin sensitivity in subjects treated with insulin needs further validation. In patients with severely impaired beta cell function, HOMA-IR may not give appropriate results.
QUICKI	QUICKI = 1/(log fasting insulin μU/mL + log fasting glucose mg/dL).	0.382 non obese, 0.331 for obese, 0.304 for diabetic individuals.	Its simplicity and ease of use. Consistent, precise index of insulin sensitivity, minimal invasive.	Complex, invasive, and costly for use in large observational studies. Normal range to be established for each lab.
Fasting insulin	–	< 25 mIU/L	Detects insulin resistance before clinical disease appears. Elevated fasting insulin levels are considered an important biomarker for IR and are associated with several health implications.	Fasting insulin levels and IR may not be the same in all individuals, Fasting insulin levels can be affected by factors such as obesity, physical activity, and genetics. Lack of standard of the insulin assay procedure.
Fasting C-peptide	–	0.9–3.0 ng/mL	Utilized to assess the basal insulin secretion of the body, prognostic indicators, and fasting C-peptide values can give information about beta cell function.	It cannot give an overall picture of IR. Limited sensitivity, variability, limited specificity, indirect measure.
Adiponectin levels	–	3.9–24.5 μg/mL in males. 5.0–38.8 μg/mL in female.	Screening and diagnosis, of IR, Prognosis, and risk assessment.	Adiponectin produced and released by adipose tissue is influenced by adipocyte size and function which is altered in obese individuals. Limited specificity. Complex regulation. Limited predictive value.
Triglyceride to glucose index	TyG index = Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]	4–8	Highly sensitive and specific, Reliable indicator, and diagnostic tool for assessing MS.	Limited clinical utility, not a direct measure of IR, population variability.

\*I<sub>mean</sub>, Average steady-state plasma insulin response (μU/mL); MCR, metabolic clearance rate of glucose (mL/kg/min)

develop more accurate and reliable markers for IR, ultimately facilitating early detection and personalized management strategies for this prevalent metabolic disorder (Table 1).

## CONCLUSION

The exploration of IR represents a dynamic and evolving field that holds substantial promise in the arena of metabolic health assessment. The diverse array of markers ranging from traditional biochemical measures to emerging genetic and molecular indicators, underscores the complexity of IR and the multifaceted nature of its assessment. While widely utilized markers such as fasting insulin and HOMA-IR continue to serve as valuable tools, it is crucial to acknowledge their limitations and consider complementary measures to enhance accuracy and specificity. The integration of novel markers, including adiponectin, triglyceride-to-glucose ratio, and genetic variants, presents exciting avenues for refining our understanding of IR and its associated metabolic implications. As we navigate toward more personalized and precise health care, the identification of robust surrogate markers becomes

increasingly critical for early detection, risk stratification, and targeted interventions. Future research should focus on elucidating the intricate interplay between these markers and their correlation with clinical outcomes. Additionally, efforts should be directed toward standardization and validation to ensure the reliability of these markers across diverse populations.

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## REFERENCES

- Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? *Curr Opin Endocrinol Diabetes Obes*;2012;19(2):81–87. DOI: 10.1097/MED.0b013e3283514e13.
- Bikov A, Frent SM, Meszaros M, et al. Triglyceride-glucose index in non-diabetic, non-obese patients with obstructive sleep apnoea. *J Clin Med* 2021;10(9):1932. DOI: 10.3390/jcm10091932.



3. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: A method for quantifying insulin secretion and resistance. *Am J Physiol Endocrinol Metab* 1979;6:163–237. DOI: 10.1152/ajpendo.1979.237.3.E214.
4. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord* 2008;6(4):299–304. DOI: 10.1089/met.2008.0034.
5. Tabassum M, Mozaffar M, Rahman MM, et al. Triglycerides and glucose index as potential marker of metabolic syndrome. *Int J Hum Heal Sci* 2021;5(1):85–89. DOI: <http://dx.doi.org/10.31344/ijhhs.v5i1.239>.
6. Khan SH, Sobia F, Niazi NK, et al. Metabolic clustering of risk factors: Evaluation of Triglyceride-glucose index (TyG index) for evaluation of insulin resistance. *Diabetol Metab Syndr* 2018;10:74. DOI: 10.1186/s13098-018-0376-8.
7. Sesti G. Pathophysiology of insulin resistance. *Best Pract Res Clin Endocrinol Metab* 2006;20(4):665–679. DOI: <https://doi.org/10.1016/j.beem.2006.09.007>.
8. Unger G, Benozzi SF, Perruzza F, et al. Triglycerides and glucose index: A useful indicator of insulin resistance. *Endocrinol Nutr* 2014;61(10):533–540. DOI: 10.1016/j.endonu.2014.06.009.
9. Minokoshi Y, Kahn CR, Kahn BB. Tissue-specific ablation of the GLUT4 glucose transporter or the insulin receptor challenges assumptions about insulin action and glucose homeostasis. *J Biol Chem* 2003;278(36):33609–33612. DOI: 10.1074/jbc.R300019200.
10. Hanhineva K, Törrönen R, Bondia-Pons I, et al. Impact of dietary polyphenols on carbohydrate metabolism. *Int J Mol Sci* 2010;11(4):1365–1402. DOI: 10.3390/ijms11041365.
11. Bays H, Mandarino L, DeFronzo RA. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: Peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. *J Clin Endocrinol Metab* 2004;89(2):463–478. DOI: <https://doi.org/10.1210/jc.2003-030723>.
12. Dandona P, Aljada A, Chaudhuri A, et al. Metabolic syndrome: A comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* 2005;111(11):1448–1454. DOI: 10.1161/01.CIR.0000158483.13093.9D.
13. Bhoi SK, Kalita J, Misra UK. Metabolic syndrome and insulin resistance in migraine. *J Headache Pain* 2012;13(4):321–326. DOI: 10.1007/s10194-012-0416-y.
14. Roberts CK, Hevener AL, Barnard RJ. Metabolic syndrome and insulin resistance: Underlying causes and modification by exercise training. *Compr Physiol* 2013;3(1):1–58. DOI: 10.1002/cphy.c110062.
15. Di Pino A, DeFronzo RA. Insulin resistance and atherosclerosis: Implications for insulin-sensitizing agents. *Endocr Rev* 2019;40(6):1447–1467. DOI: 10.1210/er.2018-00141.
16. Diamanti-Kandaraki E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: An update on mechanisms and implications. *Endocr Rev* 2012;33(6):981–1030. DOI: 10.1210/er.2011-1034.
17. Park KH, Kim JY, Ahn CW, et al. Polycystic ovarian syndrome (PCOS) and insulin resistance. *Int J Gynecol Obstet* 2001;74(3):261–267. DOI: 10.1016/s0020-7292(01)00442-8.
18. Qureshi K, Abrams GA. Metabolic liver disease of obesity and role of adipose tissue in the pathogenesis of nonalcoholic fatty liver disease. *World J Gastroenterol* 2007;13(26):3540–3553. DOI: 10.3748/wjg.v13.i26.3540.
19. Watt MJ, Miotto PM, De Nardo W, et al. The liver as an endocrine organ—Linking NAFLD and insulin resistance. *Endocr Rev* 2019;40(5):1367–1393. DOI: 10.1210/er.2019-00034.
20. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44(3):870–947. DOI: 10.1161/STR.0b013e318284056a.
21. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34(28):2159–2219. DOI: 10.1093/eurheartj/ehf151.
22. Zhao X, An X, Yang C, et al. The crucial role and mechanism of insulin resistance in metabolic disease. *Front Endocrinol (Lausanne)* 2023;14:1149239. DOI: 10.3389/fendo.2023.1149239.
23. Ormazabal V, Nair S, Elfeky O, et al. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol* 2018;17(1):122. DOI: 10.1186/s12933-018-0762-4.
24. Gutch M, Kumar S, Razi SM, et al. Assessment of insulin sensitivity/resistance. *Indian J Endocrinol Metab* 2015;19(1):160–164. DOI: 10.4103/2230-8210.146874.
25. Miles PDG, Li S, Hart M, et al. Mechanisms of insulin resistance in experimental hyperinsulinemic dogs. *J Clin Invest* 1998;101(1):202–211. DOI: 10.1172/JCI1256.
26. Tam CS, Xie W, Johnson WD, et al. Defining insulin resistance from hyperinsulinemic-euglycemic clamps. *Diabetes Care* 2012;35(7):1605–1610. DOI: 10.2337/dc11-2339.
27. Yokoyama H, Emoto M, Fujiwara S, et al. Quantitative insulin sensitivity check index and the reciprocal index of homeostasis model assessment in normal range weight and moderately obese type 2 diabetic patients. *Diabetes Care* 2014;26(8):2426–2432. DOI: 10.2337/diacare.26.8.2426.
28. Kishida K, Funahashi T, Shimomura I. Adiponectin as a routine clinical biomarker. *Best Pract Res Clin Endocrinol Metab* 2023;28(1):119–130. DOI: <https://doi.org/10.1016/j.beem.2013.08.006>.
29. Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *J Mol Sci* 2017;18(6):1321. DOI: <https://doi.org/10.3390/ijms18061321>.
30. Schöndorf T, Maiworm A, Emmison N, et al. Biological background and role of adiponectin as marker for insulin resistance and cardiovascular risk. *Clin Lab* 2005;51(9–10):489–494. PMID: 16285470.
31. Qu HQ, Li Q, Rentfro AR, et al. The definition of insulin resistance using HOMA-IR for americans of mexican descent using machine learning. *PLoS One* 2011;6(6):e21041. DOI: 10.1371/journal.pone.0021041.
32. Tahapary DL, Pratisthita LB, Fitri NA, et al. Challenges in the diagnosis of insulin resistance: Focusing on the role of HOMA-IR and Triglyceride/glucose index. *Diabetes Metab Syndr* 2022;16(8):102581. DOI: 10.1016/j.dsx.2022.102581.
33. Horáková D, Štěpánek L, Janout V, et al. Optimal homeostasis model assessment of insulin resistance (HOMA-IR) cut-offs: A cross-sectional study in the Czech population. *Medicina (Kaunas)* 2019;55(5):158. DOI: <https://doi.org/10.3390/medicina55050158>.
34. Zhang X, Li J, Zheng S, et al. Fasting insulin, insulin resistance, and risk of cardiovascular or all-cause mortality in non-diabetic adults: A meta-analysis. *Biosci Rep* 2017;37(5):BSR20170947. DOI: <https://doi.org/10.1042/BSR20170947>.
35. Sasaki N, Ozono R, Higashi Y, et al. Association of insulin resistance, plasma glucose level, and serum insulin level with hypertension in a population with different stages of impaired glucose metabolism. *J Am Heart Assoc* 2020;9(7):e015546. DOI: 10.1161/JAHA.119.015546.
36. Laakso M. How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 1993;137(9):959–965. DOI: 10.1093/oxfordjournals.aje.a116768.
37. Olefsky J, Farquhar JW, Reaven G. Relationship between fasting plasma insulin level and resistance to insulin mediated glucose uptake in normal and diabetic subjects. *Diabetes* 1973;22(7):507–513. DOI: 10.2337/diab.22.7.507.
38. Muniyappa R, Lee S, Chen H, et al. Current approaches for assessing insulin sensitivity and resistance in vivo: Advantages, limitations, and appropriate usage. *Am J Physiol Endocrinol Metab* 2008;294(1):E15–E26. DOI: 10.1152/ajpendo.00645.2007.
39. Quon MJ. Limitations of the fasting glucose to insulin ratio as an index of insulin sensitivity. *J Clin Endocrinol Metab* 2001;86(10):4615–4617. DOI: 10.1210/jcem.86.10.7952.
40. Khan HA, Sobki SH, Ekhzaimy A, et al. Biomarker potential of C-peptide for screening of insulin resistance in diabetic and non-diabetic individuals. *Saudi J Biol Sci* 2018;25(8):1729–1732. DOI: 10.1016/j.sjbs.2018.05.027.



41. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32(7):1335–1343. DOI: 10.2337/dc09-9032.
42. Chen H, Sullivan G, Yue LQ, et al. QUICKI is a useful index of insulin sensitivity in subjects with hypertension. *Am J Physiol Endocrinol Metab* 2003;284(4):E804–812. DOI: 10.1152/ajpendo.00330.2002.
43. Chen H, Sullivan G, Quon MJ. Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. *Diabetes* 2005;54(7):1914–1925. DOI: 10.2337/diabetes.54.7.1914.
44. Tao LC, Xu JN, Wang TT, et al. Triglyceride-glucose index as a marker in cardiovascular diseases: Landscape and limitations. *Cardiovasc Diabetol* 2022;21(1):68. DOI: 10.1186/s12933-022-01511-x.
45. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: Its etiology, effects and treatment. *CMAJ* 2007;176(8):1113–1120. DOI: 10.1503/cmaj.060963.
46. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab* 2010;95(7):3347–3351. DOI: 10.1210/jc.2010-0288.
47. Sánchez-García A, Rodríguez-Gutiérrez R, Mancillas-Adame L, et al. Diagnostic accuracy of the triglyceride and glucose index for insulin resistance: A systematic review. *Int J Endocrinol* 2020;2020:4678526. DOI: 10.1155/2020/4678526.
48. Lee J, Kim B, Kim W, et al. Lipid indices as simple and clinically useful surrogate markers for insulin resistance in the U.S. population. *Sci Rep* 2021;11(1):2366. DOI: <https://doi.org/10.1038/s41598-021-82053-2>.
49. Huang R, Cheng Z, Jin X, et al. Usefulness of four surrogate indexes of insulin resistance in middle-aged population in Hefei, China. *Ann Med* 2022;54(1):622–632. DOI: 10.1080/07853890.2022.2039956.
50. Rajappa M, Sridhar MG, Balachander J, et al. Lipoprotein ratios as surrogate markers for insulin resistance in south indians with normoglycemic nondiabetic acute coronary syndrome. *ISRN Endocrinol* 2014;2014:981524. DOI: 10.1155/2014/981524.
51. Oliveri A, Rebernick RJ, Kuppa A, et al. Comprehensive genetic study of the insulin resistance marker TG:HDL-C in the UK Biobank. *Nat Genet* 2024;56(2):212–221. DOI: 10.1038/s41588-023-01625-2.
52. Perumalsamy S, Huri HZ, Abdullah BM, et al. Genetic markers of insulin resistance and atherosclerosis in type 2 diabetes mellitus patients with coronary artery disease. *Metabolites* 2023;13(3):427. DOI: 10.3390/metabo13030427.
53. Lee S, Ahn J, Park J, et al. Genetic Diversity of Insulin Resistance and Metabolic Syndrome. In: *Genetic Variation*. IntechOpen; 2021. Available from: <http://dx.doi.org/10.5772/intechopen.93906>.
54. Lu M, Li P, Bandyopadhyay G, et al. Characterization of a novel glucokinase activator in rat and mouse models. *PLoS One* 2014;9(2):e88431. DOI: 10.1371/journal.pone.0088431.
55. Kawashima Y, Nagai H, Konno R, et al. Single-shot 10k proteome approach: Over 10,000 protein identifications by data-independent acquisition-based single-shot proteomics with ion mobility spectrometry. *J Proteome Res* 2022;21(6):1418–1427. DOI: 10.1021/acs.jproteome.2c00023.
56. Stahelin RV. Lipid binding domains: More than simple lipid effectors. *J Lipid Res* 2009;50(Suppl):S299–S304. DOI: 10.1194/jlr.R800078-JLR200.
57. Hu YH, Meyer K, Lulla A, et al. Gut microbiome and stages of diabetes in middle-aged adults: CARDIA microbiome study. *Nutr Metab* 2023;20(1):3. DOI: 10.1186/s12986-022-00721-0.
58. Takeuchi T, Kubota T, Nakanishi Y, et al. Gut microbial carbohydrate metabolism contributes to insulin resistance. *Nature* 2023;621(7978):389–395. DOI: <https://doi.org/10.1038/s41586-023-06466-x>.
59. Ripoche M, Bouchard C, Irace-Cima A, et al. Current and future distribution of Ixodes scapularis ticks in Québec: Field validation of a predictive model. *PLoS One* 2022;17(2):e0263243. DOI: 10.1371/journal.pone.0263243.
60. Macalli M, Navarro M, Orri M, et al. A machine learning approach for predicting suicidal thoughts and behaviors among college students. *Sci Rep* 2021;11(1):11363. DOI: <https://doi.org/10.1038/s41598-021-90728-z>.
61. Rashid MM, Askari MR, Chen C, et al. Artificial intelligence algorithms for treatment of diabetes. *Algorithms* 2022;15(9):299. DOI: <https://doi.org/10.3390/a15090299>.
62. Jacobs PG, Herrero P, Facchinetti A, et al. Artificial intelligence and machine learning for improving glycemic control in diabetes: Best practices, pitfalls, and opportunities. *IEEE Rev Biomed Eng* 2024;17:19–41. DOI: 10.1109/RBME.2023.3331297.
63. Tsai SF, Yang CT, Liu WJ, et al. Development and validation of an insulin resistance model for a population without diabetes mellitus and its clinical implication: A prospective cohort study. *EClinicalMedicine* 2023;58:101934. DOI: 10.1016/j.eclinm.2023.101934.