REVIEW ARTICLE

Role of Triglyceride to High Density Lipoprotein (TG/HDL) Ratio as A Marker of Insulin Resistance in Adults of Central India: A Narrative Review

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DOI: 10.55489/njcm.150420243789

ABSTRACT

One of the main risk factors for the onset of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) is insulin resistance (IR). But because there aren't many easy-to-use and trustworthy biomarkers or tests, the entity is frequently under diagnosed. The present review was performed with an aim to provide the available data regarding the role or efficacy of TG/HDL ratio as an indicator of IR in adults of central India, a region popular for high prevalence of T2DM and CVD. An extensive search of all materials related to the topic was carried out in the PubMed search engine. Relevant research articles focusing on use of TG/HDL as a marker of insulin resistance published in the period 2002 to 2023 were included in the review. A total of 33 articles were selected based upon their suitability with the current review objectives and analyzed. The review concludes that TG/HDL ratio is a simple, affordable, and feasible marker of IR that can be used in economically poor regions of the India or world for screening IR and risk stratification of T2DM and CVD in adults. However, more studies are needed in India and all over the world to validate this marker and its cut-off values.

Keywords: Insulin resistance, Central India, TG/HDL ratio, lipid abnormalities

ARTICLE INFO

Financial Support: None declared
Conflict of Interest: None declared
Received: 29-01-2024, **Accepted**: 20-03-2024, **Published**: 01-04-2024
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How to cite this article: Khan K, Quazi S, Wanjari A. Role of Triglyceride to High Density Lipoprotein (TG/HDL) Ratio as A Marker of Insulin Resistance in Adults of Central India: A Narrative Review. Natl J Community Med 2024;15(4):320-326. DOI: 10.55489/njcm.150420243789

www.njcmindia.com | pISSN09763325 | eISSN22296816 | Published by Medsci Publications

INTRODUCTION

Insulin resistance (IR) is a condition in which cells do not respond to the insulin hormone in a physiological way and to compensate this, the body is secreting a large amount of insulin.[1] This alteration leads to development of obesity, prediabetes, type 2 diabetes mellitus (T2DM), hypertension (HTN), dyslipidemia, and various cardiovascular diseases (CVD).[1–3] The prevalence of IR in India is estimated between 9% to 32% or more in the general population, depending on the criteria and methods used to measure it.[4,5] The prevalence of obesity in India is around 30.5%.[6] Whereas the prevalence of IR reported in non-obese Indians varies from 11% to 43%.[7] It is more common in cities compared to rural areas, and in the middle to high-class income strata than the low-income.[4] Migration from rural to urban areas in India is contributing significantly to urbanization and potentially increases the risks of obesity and diabetes.[8,9]Similarly, socioeconomic status and insulin resistance are positively corelated in many studies.[9–11] IR results in obesity or more precisely central obesity, hypertension, prediabetes, T2DM, dyslipidemia, low HDL, and high TG levels, ultimately leading to a high incidence of (CVD).[1,4] Pertaining to the importance of IR, various markers of IR have been developed, such as euglycemic-hyperinsulinemia clamp test, the homeostasis model assessment for IR (HOMA-IR) or the oral glucose tolerance test (OGTT).[12]

However, these methods are complex, invasive, or expensive or impractical for day-to-day practice or large-scale screening or epidemiological studies.[12] therefore, there is a dire need for simple, inexpensive, feasible, and reliable surrogate markers of IR that can be easily used in medical practice and research. The ratio of triglycerides (TG) to high-density lipoproteins (TG/HDL) is one of the proposed surrogate markers of IR. It reflects the balance between lipolysis and lipoprotein clearance in the body, both of which are influenced by IR.[2] Several studies have shown that the TG/HDL ratio is positively correlated with the IR measured by clamp or HOMA-IR and that it can predict the risk of developing T2DM, metabolic syndrome, or CVD.[12]

However, the clinical utility and cut-off values of this marker change, depending on the different populations, their ethnicity, genetic factors, demographic area, foods, and lifestyle.[4] Central Indians are exposed to complex interactions between lifestyle and environmental factors, a wide range of genetic variations, and a high prevalence of metabolic syndrome, T2DM and other CVD risk factors. The role of TG/HDL as an indication of IR in this population has received relatively late and little research attention. Therefore, the objective of this narrative review is to address the possible implications and limitations of using this marker in this situation, as well as to compile the information on TG/HDL and IR that is currently available to adults in central India.

METHODOLOGY

An extensive search of all materials related to the topic was carried out in the PubMed search engine. Relevant research articles focusing on use of TG/HDL as a marker of insulin resistance published in the period 2002 to 2023 were included in the review. A total of 38 studies similar to current study objectives was identified initially, of which, five were excluded due to the unavailability of the complete version of the articles. Overall, 33 articles were selected based upon their suitability with the current review objectives and analyzed.

Physiological basis of the TG / HDL ratio: The lipid profile is a crucial component of the assessment of cardiovascular health. It comprises several elements, each of which plays a unique role in metabolic processes, especially regarding IR and atherosclerosis.[15,16] Fats produced from extra calories and stored in adipose tissue are called TG. They are an essential source of energy, and, when IR develops, their levels rise due to increased lipolysis and poor glucose utilization.[17] Elevated TG facilitate the development of arterial plaque and the process of atherosclerosis.[14–17]

Reverse cholesterol transfer depends on high-density lipoprotein cholesterol or HDL-C or HDL which is often referred to as "good" cholesterol.[15] By bringing cholesterol to the liver from peripheral tissues for processing and elimination, HDL inhibits the development of arterial plaque. People with genetic susceptibility and IR typically have lower HDL levels, increasing the risk of cardiovascular disease because arterial cholesterol is not adequately eliminated.[14–16]. Low-density lipoprotein cholesterol or LDL-C or LDL is more atherogenic. They transport cholesterol to cells and vessels throughout the body, leading to their accumulation, arterial plaque formation, and successive cardiovascular consequences.[18] IR increases the formation of dense LDLs from LDL, which are more prone than larger ones to produce atherosclerosis. Our routinely performed lipid profile does not include this component of LDL[15,16,18]

The physiological foundation makes it one of the best indicators of IR. The fundamental idea underlying the change in lipid metabolism is IR, which hinders the body's ability to use glucose efficiently and increases blood glucose levels, raising triglyceride levels.[16,19] On the contrary, IR associated with genetic components makes Indians more susceptible to reduced HDL cholesterol,[4] high ratio of TG to HDL cholesterol indicates a lipid imbalance in the blood. This imbalance is a powerful predictor of IR and the resulting elevated risk of heart problems.[2] As a result, this ratio provides information on the abnormalities in lipid metabolism associated with IR. It is a straightforward, practical, affordable, and therapeutically relevant surrogate diagnostic marker for the IR and CVDs.

It is important to keep in mind that various ethnic

groups may react differently to TG/HDL as an indicator of IR, requiring evaluations specific to the requirements of each ethnic group.[2,4,16]. Furthermore, it is imperative to comprehend the significance of the TG/HDL ratio about cardiovascular risk, since it not only signifies IR but is also linked to heightened cardiovascular risk because of the associated atherogenic lipid profile. This knowledge emphasizes the need for a thorough evaluation process for metabolic health, stressing the importance of monitoring the lipid profile in the management and preventing IR and related cardiovascular complications.[14,15,18]

When comparing the TG/HDL ratio with other tests, such as the glucose clamp test and the homeostatic model evaluation for IR (HOMA-IR), the former is more user-friendly, non-invasive and readily available.[13] because the TG/HDL ratio is easily obtained from standard lipid panels, it is helpful for large-scale screening, epidemiological research, rural or remote locations, and economically challenged places.[2,19] On the other hand, although the glucose clamp technique is the gold standard for determining insulin sensitivity, it is too complicated, invasive, time consuming, and unfeasible for everyday use and for research study use. Except for the expense of fasting insulin level, HOMA-IR, on the other hand, offers a direct evaluation of IR based on fasting insulin and glucose levels. According to some research, the TG/HDL ratio is a highly useful indicator of IR (IR) in people of normal weight, particularly women. It is also an excellent indicator of obesity, overweight, or prediabetics.[20–22]

Clinical evidence from different epidemiological studies: In a Mexican urban middle class population, the TG/HDL ratio is an important cardiovascular risk marker (IR marker) that should be included in the high-risk scores for CVD events.[23]

In their investigation, **Ren et al. (2016)**[14] discovered a favourable correlation between TG/HDL and IR in Chinese patients with newly diagnosed T2DM. **Gong et al. (2021)**[21] examined the relationship between IR (IR), cardiovascular disease (CVD) risk factors, and the TG/HDL ratio in different US populations by analyzing information from the 2009–2018 National Health and Nutrition Examination Survey. The TG/HDL ratio is a marker of both IR and unfavorable cardiovascular events, according to a cross-sectional study involving 49,696 participants. Within the same ethnic groups, there is a higher link between the ratio and alcoholics, women, diabetics, prediabetics, and smokers.

The study by **Hajian-Tilaki et al. (2020)**[24] to examine the predictive power of two lipid ratios for CVD events, TG/HDL and LDL/HDL, held in Babol, in the north of Iran, which involved 567 individuals 40 years or older at risk of a CVD event according to the ACC / AHA risk model, showed that LDL/HDL and TG/HDL were both highly significant predictors of CVD risk in men, as depicted in Table 1. The ideal cut-off value for TG/HDL was found to be 3.6, resulting in 75% sensitivity and 39% specificity. Furthermore, the TG/HDL ratio in females strongly predicted the CVD risk, while the LDL/HDL ratio did not. In women, a threshold of 3.4 for the TG/HDL ratio produced a sensitivity of 82% and a specificity of 51%. According to the study, the area under the curve (AUC) for TG/HDL and LDL/HDL in men is identical, indicating that they are equally accurate in predicting the risk of cardiovascular disease. However, the AUC for TG / HDL was noticeably higher for women than for LDL/HDL. This suggests that the ideal threshold values for certain lipid ratios may vary according to gender and ethnicity.[25] **Park et al.**[19] also demonstrated that TG/HDL has high sensitivity and specificity as a diagnostic marker for IR and CVD events, such as ischemic heart disease (IHD); women had more positive correlations than men.

Table 1: Findings from selected articles

Authors	Year	Key Findings
Martínez-Marroquín et al.[23]	2023	Emphasizes the importance of the TG / HDL ratio as a cardiovascular risk marker in the urban middle-class population; inclusion of this marker in high-risk scoring system for CVD events.
Ren et al.[14]	2016	Discovered a favorable correlation between TG/HDL and IR (IR) in newly diagnosed Chinese patients.
Gong et al.[21]	2021	Examined relationship between IR, CVD risk factors, and TG/HDL ratio in different US populations; markers for IR and unfavorable cardiovascular events; higher links in specific groups.
Hajian-Tilaki et al.[24]	2020	Investigated the predictive power of the TG/HDL and LDL/HDL ratios for CVD events in a north Iranian population; both ratios are highly significant predictors in men; gender-specific thresholds and variations in AUC.
Park et al.[19]	2021	Demonstrated high sensitivity and specificity of TG/HDL as a diagnostic marker for IR and CVD events, especially in females; positive correlations are more prominent in women than in men.

DISCUSSION

According to established narrative review guidelines, this examination aims to elucidate the potential implications and limitations inherent in the application of the TG/HDL ratio in a specific clinical context, particularly highlighting its correlation with IR, type 2 diabetes mellitus (T2DM), and cardiovascular dis-

ease (CVD) among the population of central India. A comprehensive analysis of the pertinent literature revealed a robust and statistically significant positive association between TG/HDL and IR, ascertained through a variety of diagnostic methodologies.[26] This correlation persisted as significant, transcending variations in age, sex, ethnicity, and geographical location, even after adjustment for a spectrum of potential confounder variables.[27]

Most of the research that made up this review showed a positive and substantial correlation between T2DM and CVD, and the TG/HDL ratio. Males were more correlated than females, while Mexican Americans and non-Hispanic whites were more correlated than non-Hispanic blacks. Even after taking into account other risk variables and potential confounders, the connection was still strong.[28] We also found that some studies demonstrated this marker better for women than for men. In addition, various habits, such as alcohol consumption, increase its association with IR and CVD. The reason behind global variation is a different lifestyle, eating habits, personal habits, genetics, metabolism pattern, and ethnicity.

Although the cut-off values for the TG/HDL ratio varied throughout the research, they generally fell between 1.5 and 5.0 to detect IR, predict T2DM, and indicate CVD. As a marker of IR, T2DM, and CVD, the TG/HDL-C ratio had moderate to high sensitivity and specificity, depending on the cut-off values and reference methods used.

The study by **Mohan V. et al. (2004)**[4] emphasizes how diabetes is becoming a more serious concern in India and worldwide, focusing on how fast it is spreading. By 2025, non-industrialized nations such as China and India will account for a sizable share of the global population with diabetes. Due to lifestyle changes caused by industrialization and urban migration, T2DM is becoming increasingly common among Indian migrants and is alarmingly high in India's cities. The trend for causation of obesity, especially central obesity, is driven by factors such as lack of physical activity and a shift in dietary habits towards meals that are high in calories, fat, and sugar.[29]

Main causes of the diabetes epidemic in India:

Increased IR: Compared with Caucasians, Indians have greater levels of IR. Elevated IR contributes significantly to the high prevalence of diabetes together with other components of the metabolic syndrome.[30]

Genetic factors: Genetic factors play a pivotal role in the diabetes epidemic in India, contributing significantly to the increased prevalence of the disease. There is a notable genetic predisposition to diabetes, characterized by specific variants and mutations identified as crucial contributors to an individual's vulnerability to both type 1 and T2DM. The Indian population displays a unique genetic profile, featuring a higher occurrence of particular risk alleles compared to other ethnic groups. This genetic diversity enhances the population's susceptibility to diabetes.[31]

Environmental Factors and Urbanization: Rapid socioeconomic development and urbanization in India have led to changes in lifestyle. Factors such as altered diet, reduced physical activity, and higher income contribute to the increase in the incidence of diabetes. These lifestyle changes have also led to a rise in obesity rates, further exacerbating the diabetes epidemic.[32] Additionally, the increased availability and consumption of processed and sugary foods have significantly impacted the overall health of the population. As a result, there is a pressing need for public health initiatives and education programs to promote healthier lifestyles and combat the growing diabetes crisis in India.[33] The issue does not only affect adults; children and adolescents are also experiencing an alarming rise in type 2 diabetes, which is indicative of global patterns caused by industrialization and globalization. Increasing physical activity and reducing obesity are two interventions to combat this increasing health concern; adults and children must reverse the trend.[34] Various study confirms that rural-to-urban migration is associated with a marked increase in obesity and diabetes, attributing these conditions to lifestyle changes post-migration, such as decreased physical activity and increased fat intake.[4,8,9,29] Contrary to expectations, migrants did not exhibit intermediate prevalence rates of obesity and diabetes between urban and rural residents, and the hypothesis that longer residence in urban areas correlates with higher prevalence rates received minimal support.[4,9,10]

Studies have showed the distinct impacts of intrinsic versus added sugars on metabolic health, with a particular focus on fruit juices versus sugary solutions.[35,36]

Mediterranean diet's potential for improving insulin sensitivity and metabolic health, contrasted with high-protein diets' effectiveness in specific populations of central India.[37]

Chronic energy oversupply from food, coupled with insufficient physical activity, leads to overweight, abdominal adiposity, insulin resistance, and eventually Type 2 Diabetes Mellitus (T2DM).[38,39]

Conversely, energy-reduced diets usually facilitate weight loss, diminishing abdominal fat mass and insulin resistance. However, sustained weight loss is challenging, especially in T2DM patients due to their unique metabolic characteristics. Various dietary strategies have been proposed, including those modifying fat, protein, fibre and carbohydrate intake.[37–39]

Codero, et al. (2009)[2] found that TG/HDL, independent of body mass index, has a strong predictive value for an initial coronary event and is an indirect indication of IR and cardiovascular events. Additionally, a high TG/HDL ratio has been linked to an increased risk of developing metabolic syndrome.

Monitoring and maintaining a healthy TG/HDL ratio is crucial in assessing an individual's overall cardiovascular health and identifying potential risks for future coronary events. Similarly, **Ren et al. (2016)**[14] identified TG/HDL ratio is a reliable indicator of IR and diabetes in Chinese adults who are not taking any medications for diabetes, dyslipidemia, or obesity, regardless of their waist circumference. The TG/HDL ratio can be used to identify people who may not exhibit typical indications of obesity but are nonetheless at risk of developing IR and diabetes. Patients with T2DM are at significant risk for macrovascular complications, which are the leading cause of death, according to a study by **Di Pino et al.**[27]. There is still a substantial amount of unaccounted for CVD risk, even with the successful treatment of recognized risk factors (dyslipidemia, hypertension, procoagulant disease). A set of interrelated cardiometabolic risk factors linked to IR can be assessed by the ratio of TG to HDL.

Hajian-Tilaki et al.[24] to examine the predictive power of two lipid ratios for cardiovascular disease (CVD) events, the triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-C) and the low-density lipoprotein cholesterol to HDL-C ratio (LDL-C/HDL-C), conducted in Babol, in the north of Iran, that involved 567 individuals 40 years or older using the risk of a CVD event according to the ACC / AHA risk model, showed that TG/HDL and LDL/HDL were extremely significant markers of CVD risk in men. The optimal cut-off value for the TG/HDL was determined to be 3.6, resulting in 75% sensitivity and 39% specificity. Furthermore, the TG/HDL ratio in women significantly predicted the CVD risk, whereas LDL/HDL did not. In women, a threshold of 3.4 for the TG/HDL-C ratio yielded 82% sensitivity and 51% specificity. The study found that in men, LDL/HDL and TG/HDL have the same area under the Curve (AUC), suggesting that they are equally accurate in predicting the risk of cardiovascular disease. However, for women, the AUC for TG/HDL was significantly higher than for LDL/HDL. Gender and ethnicity could influence the optimal threshold values for different lipid ratios. **Park et al. (2021)**[15] stated that TG/HDL had high sensitivity and specificity as a diagnostic marker of IR and CVD events, such as ischemic heart disease (IHD); women had more positive correlations than men. This suggests that TG/HDL ratio may be a more reliable indicator of IR and cardiovascular disease in women.

Gong et al. (2021)[21] examined the relationship between IR, CVD risk factors, and the TG/HDL ratio in different US populations by analysing data from the 2009–2018 National Health and Nutrition Examination Survey. The TG/HDL ratio is a marker of both IR and unfavourable cardiovascular events, according to a cross-sectional study involving 49,696 participants. Within the same ethnic groups, there is a higher link between the ratio and alcoholics, women, diabetics, prediabetics, and smokers. A study by **Deusdara et al. (2022)**[13] found that obesity, overweight, and waist circumference had a positive correlation with IR markers (TG/HDL, and others) among Brazilian adolescent students.

Kosmas et al. (2023)[40] showed that atherosclerosis which is defined as the accumulation of lipid plaques in blood vessels, causes atherosclerotic cardiovascular disease (ASCVD), Spectrum of term ASCVD includes cerebrovascular disease, coronary artery disease and peripheral arterial disease. They found that dyslipidemia, or abnormal lipid metabolism, is a major factor in the development of plaque. The study also suggested the TG/HDL ratio as a novel biomarker to evaluate the risk of metabolic syndrome (MetS) and CVD, connecting elevated plasma TG levels and low HDL levels to both conditions. In a study by **Ormazabal et al. (2024)**[24] they found that the IR calculated by TG/HDL has a positive correlation with IHD, a CVD event.

Personalized medicine and its clinical implications: Due to its ease of use and practicality, the TG/HDL ratio is a valuable tool in clinical settings, particularly where other diagnostic procedures are not feasible. Its association with IR and cardiovascular risk factors is supported by various researches and is helpful in diagnosing and stratifying the risk of T2DM and CVD in adults. The usefulness of the ratio can vary between demographic and ethnic groups, requiring custom methods for various populations.

Limitations

TG/HDL, as a marker of IR, has certain limitations for different ethnic groups, the reason being different lifestyles, diet patterns, sex, genetics, habits, and lipid metabolism patterns of different populations.[19,21,41] Population-specific studies on a large scale from different parts of the world and their meta-analysis will be required to address this issue. Furthermore, identification of its cut-off vale and its role in the development of IR in particular population should be sought.[14,23,42]

Conclusion

TG/HDL ratio can be easily incorporated into clinical practice and research as a simple, low-cost surrogate marker of IR, T2DM, and CVD. The review emphasizes the need for more studies to confirm, standardize, and elucidate the relationship between the TG/HDL ratio and IR, T2DM, and CVD in different subpopulations of central India. It also highlights the drawbacks and difficulties of using the ratio as a marker of IR, T2DM, and CVD in this context. Given the high prevalence of IR, T2DM, and CVD in this area, as well as the considerable genetic susceptibility and intricate interactions between these disorders, the TG and HDL get significantly affected, thus, reflected in the ratio. So, TG/HDL can significantly help in prevention, diagnosis, and treatment of these conditions.

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