Triglyceride/High-Density Lipoprotein Cholesterol Ratio in Metabolic Syndrome

Subjects: Cardiac & Cardiovascular Systems
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Increased plasma triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C) levels have been associated with metabolic syndrome (MetS) and cardiovascular disease (CVD), and their ratio, TG/HDL-C, has been proposed as a novel biomarker for predicting the risk of both clinical entities.

triglycerides HDL-C TG/HDL-C ratio risk marker

1. Introduction

The pathophysiology of atherosclerosis depends vastly on lipid transportation along with inflammation.

Inflammation plays a crucial role in the pathogenesis of cardiovascular disease (CVD), as it has been linked with both the initiation and progression of atherosclerosis [1][2]. Several pro-inflammatory cytokines, such as the C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), have been unequivocally shown to promote both insulin resistance (IR) and atherogenesis [1][2][3]. Furthermore, inflammation plays a major role in the pathogenesis of chronic lung disease [4], as well as in the pathogenesis of chronic kidney disease (CKD), also including the development of malnutrition–inflammation–atherosclerosis syndrome (MIA), which is one of the causes of increased mortality in CKD [3][5]

The formation and subsequent potential rupture of unstable atherosclerotic plaques is mediated by disruptions in the physiology of lipid metabolism. Macrophages take up and accumulate oxidized triglycerides (oxTGs) and cholesterol particles in their cytoplasm, a procedure that effectuates their transformation into lipid-enriched cells named foam cells. The latter are the cornerstone in atherogenesis, which precedes atherosclerotic cardiovascular disease (ASCVD). Coronary artery disease (CAD), peripheral vascular disease (PAD) and cerebrovascular disease (CCVD) constitute the three aspects of ASCVD. Hence, defects in lipid metabolism induce atherogenesis and an increase in the risk of CVD [6]. According to WHO, 32% of global deaths in 2019 were attributed to CVD; CAD and CVA were held responsible for 85% of them [7].

Ample clinical evidence suggests a strong association between elevated low-density lipoprotein cholesterol (LDL-C) and poor cardiovascular outcomes [8]. Statins are the standard-of-care for managing LDL-C levels. Aggressive lowering of LDL-C, even beyond the previously established cut-off target of 70 mg/dl, has been demonstrated to ameliorate cardiovascular outcomes [9][10][11][12][13]. Nevertheless, a noteworthy subset of patients remains in peril

for CVD events, in spite of optimal LDL-C control [14]. This residual metabolic risk could be attributed to various atherogenic processes that continue to exist even after aggressive LDL-C lowering and is plausibly correlated with certain novel biomarkers, addressing new data concerning the optimal holistic approach of this specific subset of patients [15]. An association between increased plasma triglyceride (TG) and decreased high-density lipoprotein cholesterol (HDL-C) levels with metabolic syndrome (MetS) and CVD (including CAD, PAD and CCVD) has been proposed. More specifically, a descriptive parameter known as triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio has been strongly correlated with insulin resistance (IR) and central obesity, both of them being aspects of the MetS, which can enhance the risk of CVD [16]. HDL-C has been linked to cardioprotective effects via its antioxidant and anti-inflammatory properties [6]. The current literature supports that decreased HDL-C levels predispose to CVD, although interventions targeting an increase in HDL-C levels per se have not been proven successful in decreasing the risk of CVD [17]. It is well known that atherosclerosis is a significant CVD-related mortality factor in patients with end-stage renal disease, as it appears to be about 10 to 30 times more prevalent compared to the general population. A retrospective study including 973 patients in peritoneal dialysis (PD) concluded that a higher serum TG/HDL-C ratio was an independent variable in terms of predicting all-cause and CVD mortality in young and older PD patients [18].

Bearing in mind the existing evidence, the TG/HDL-C ratio could arise as a promising marker for the assessment of CVD risk, morbidity and mortality and may become a valuable tool in terms of addressing strategies for primary and secondary prevention [19].

2. Triglyceride/HDL-C Ratio in Metabolic Syndrome

The National Cholesterol Education Program Adult Treatment Panel III (ATP III) defines metabolic syndrome as central obesity (waist circumference: >102 cm in men and >88 cm in women), abnormal lipid panel (HDL-C <40 mg/dl in men and <50 mg/dl in women and TG ≥150 mg/dl), elevated blood pressure (systolic blood pressure [SBP] ≥130 mmHg or diastolic blood pressure [DBP] ≥85 mmHg) and insulin resistance/glucose intolerance (fasting glucose ≥100 mg/dl). The diagnosis is clear when at least three of these criteria are met [20][21]. The worldwide MetS prevalence is estimated to be from 20 to 25% in the adult population [21]. MetS augments the likelihood of CVD, diabetes mellitus (DM) and chronic kidney disease (CKD) [22]. Whilst clinicians have established a connection between elevated serum levels of LDL-C and CVD, the identification of biomarkers applicable for MetS and its active part in atherogenesis may be challenging [23]. For the past decade, extensive research has been conducted regarding the interlink between TGs and other lipoproteins, yet has not been entirely fruitful. Recent studies have demonstrated that the TG/HDL-C ratio is a convenient tool for detecting IR, one of the main components of MetS. This tool is practical and a potential alternative to the conventional insulin assay, allowing an early identification of the cardiometabolic hazards before the advent of clinical manifestations and complications [24][25][26].

Scientific research data support the positive correlation between MetS, CVD and the value of the TG/HDL-C ratio. An early analysis by Mc Laughin et al. in 2003 focused on the relation between TG/HDL-C ratio and cardiometabolic risk at a cut-off point of 3.0 units, for both men and women. A total of 258 overweight volunteers (body mass index, [BMI] ≥25 kg/m^2) with no previous diagnosis of hypertension or diabetes were included. Plasma

TG levels, TG/HDL-C ratio and insulin concentration were measured. Data concluded that the use of TG/HDL-C ratio in overweight patients could be a valuable tool for identifying insulin resistance in those patients, which poses them at an increased risk for CVD [25].

In another recent cross-sectional study involving over 5000 Iranian participants, anthropometric measures and blood pressure were taken and the patients were categorized according to their lipid ratios (total cholesterol/HDL-C ratio, LDL-C/HDL-C ratio and TG/HDL-C ratio). After adjusting for various variables (age, gender, body mass index and past medical history), the researchers concluded that the TG/HDL-C was the best indicator for identifying metabolic syndrome compared to the other ratios [22]. Another study in Iran demonstrated that the high TG/HDL-C ratio was associated with a 2.12 times increased risk of developing metabolic syndrome, using a cut-off point of 4.03 for males and 2.86 for females [27].

In 2021, a cross-sectional study was conducted in the elderly Chinese population, which included a total of 1267 participants ≥65 years of age. The purpose for the researchers was to investigate a correlation between TG/HDL-C ratio and MetS. They determined that TG/HDL-C ratio values exceeding the cut-off values of 1.437 for men and 1.196 for women predicted a higher risk of developing MetS [28]. Additionally, the Korean National Health and Nutrition Examination Survey conducted a large-scale study concerning the TG/HDL-C ratio and its relationship with metabolic syndrome. The mean TG/HDL-C ratio increased along with the number of MetS components. The cut-off point of the TG/HDL-C ratio for the fourth quartile was 3.52 and, after adjustment, the odds ratio (OR) for MetS in the fourth quartile compared with that of the first quartile was 29.65 in men and 20.60 in women ($P < 0.001$) [29].

Last but not least, a multicentered study in Brazil enrolled 2472 multiethnic participants free of major cardiovascular risk factors and defined the TG/HDL-C ratio cut-off value of 2.6 for men and 1.7 for women. The results of this study demonstrated that these cut-off values were reliable and showed good clinical applicability to detect cardiometabolic disorders. Moreover, these cut-off values demonstrated great sensitivity and specificity regardless of the ethnicity or age of the participants, although the black race showed lower values of the TG/HDL-C ratio, compared with other ethnic groups [26].

Undoubtedly, the TG/HDL-C ratio is a very satisfactory predictor for MetS. Nonetheless, taking into consideration the different cut-off values of multiple trials, based on ethnicity, genetics and lifestyle, the aforementioned ratio cannot be considered an absolute parameter without calibration. The cumulative risk factors are well established through the different studies; therefore, the TG/HDL-C ratio could function as an atherogenic index for MetS [30][31][32].

A summary of the results of the clinical studies relating to the TG/HDL-C ratio and Metabolic Syndrome is shown in **Table 1**.

Table 1. Summary of the results of the clinical studies relating to TG/HDL/C ratio and metabolic syndrome.

Study	Design	Method	Results
The Atherogenic Index Log (Triglyceride/HDL-Cholesterol) as a Biomarker to Identify Type 2 Diabetes Patients with Poor Glycemic Control [16]	Prospective cohort	TG/HDL-C ratio measurement	The log (TG/HDL-C) can be considered as a biomarker to predict T2D patients with poor glycemic control. The best cut-off point of log (TG/HDL-C) for the discrimination between patients with HbA1c ≥8% versus patients with HbA1c <8% determined to be 0.44.
Comparison of Lipid Ratios to Identify Metabolic Syndrome [22]	Cross-sectional	TC/HDL-C, TG/HDL-C and LDL/HDL-C ratio	The results suggest that TG/HDL-C ratio is a better marker for identifying MetS in the Iranian population.
Use of metabolic markers to identify insulin resistant overweight individuals [25]	Cross-sectional	TG, TG/HDL-C and insulin concentration	Cut-point of TG/HDL-C ratio was 3.0 for both male and female participants. The sensitivity and specificity were 64% and 68%, respectively, regarding identification of insulin resistance and diagnosis of MetS.
Reference values for the triglyceride to high-density lipoprotein ratio and its association with cardiometabolic diseases in a mixed adult population: The ELSA-Brazil [26]	Prospective cohort	Anthropometric measurement and TG/HDL-C ratio	Cut-off values of TG/HDL-C ratio were 2.6 for males and 1.7 for females, displaying great sensitivity and specificity, regardless of the ethnicity or age.
Lipid ratio as a suitable tool to identify individuals with MetS risk: A case- control study [27]	Case–control	Serum lipids and MetS criteria	High TG/HDL-C ratio increases by 2.12 times the possibility of having MetS. Its cut-off points were 4.03 for men and 2.86 for women.
High TG/HDL ratio suggests a higher risk of metabolic syndrome among an elderly Chinese population: a cross-sectional study [28]	Cross-sectional	Anthropometric parameters and blood drawn for lipid panel	TG/HDL-C ratio values exceeding the cut-off values of 1.437 for men and 1.196 for women predicted a higher risk of developing MetS.
The Relationship between the Triglyceride to High-Density Lipoprotein Cholesterol Ratio and Metabolic Syndrome [29]	Cross-sectional	Anthropometric measurements and TG/HDL-C ratio	The cut-off point of the TG/HDL-C ratio for the fourth quartile was 3.52 and, after adjustment, the OR for MetS in the fourth quartile compared with that of the first quartile was 29.65 in men and 20.60 in women ($P < 0.001$).

References

1. Christodoulidis, G.; Vittorio, T.J.; Fudim, M.; Lerakis, S.; Kosmas, C.E. Inflammation in coronary artery disease. Cardiol. Rev. 2014, 22, 279–288.
2. Kosmas, C.E.; Silverio, D.; Sourlas, A.; Montan, P.D.; Guzman, E.; Garcia, M.J. Anti-inflammatory therapy for cardiovascular disease. Ann. Transl. Med. 2019, 7, 147.
3. Kosmas, C.E.; Silverio, D.; Tsomidou, C.; Salcedo, M.D.; Montan, P.D.; Guzman, E. The Impact of Insulin Resistance and Chronic Kidney Disease on Inflammation and Cardiovascular Disease. Clin. Med. Insights Endocrinol. Diabetes 2018, 11, 1179551418792257.
4. Atamas, S.P.; Chapoval, S.P.; Keegan, A.D. Cytokines in chronic respiratory diseases. F1000 Biol. Rep. 2013, 5, 3.
5. Allawi, A.A.D. Malnutrition, inflamation and atherosclerosis (MIA syndrome) in patients with end stage renal disease on maintenance hemodialysis (a single centre experience). Diabetes Metab. Syndr. 2018, 12, 91–97.
6. Welty, F.K. How do elevated triglycerides and low HDL-cholesterol affect inflammation and atherothrombosis? Curr. Cardiol. Rep. 2013, 15, 400.
7. World Health Organization. Cardiovascular Diseases (CVDs). Available online: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed on 19 January 2023).
8. Guijarro, C.; Cosin-Sales, J. LDL cholesterol and atherosclerosis: The evidence. Clin. Investig. Arter.Publ. Off. Soc. Esp. Arterioscler. 2021, 33 (Suppl. S1), 25–32.
9. Writing, C.; Lloyd-Jones, D.M.; Morris, P.B.; Ballantyne, C.M.; Birtcher, K.K.; Covington, A.M.; DePalma, S.M.; Minissian, M.B.; Orringer, C.E.; Smith, S.C., Jr.; et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. J. Am. Coll. Cardiol. 2022, 80, 1366–1418.
10. Bavry, A.; Bhatt, B.D.; Kumbhani, D. Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk—FOURIER. Available online: https://www.acc.org/latest-in-cardiology/clinical-trials/2017/03/16/00/46/fourier (accessed on 19 January 2023).
11. Ray, K.K.; Wright, R.S.; Kallend, D.; Koenig, W.; Leiter, L.A.; Raal, F.J.; Bisch, J.A.; Richardson, T.; Jaros, M.; Wijngaard, P.L.J.; et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. N. Engl. J. Med. 2020, 382, 1507–1519.
12. Kosmas, C.E.; Munoz Estrella, A.; Sourlas, A.; Silverio, D.; Hilario, E.; Montan, P.D.; Guzman, E. Inclisiran: A New Promising Agent in the Management of Hypercholesterolemia. Diseases 2018, 6, 63.

13. Marston, N.A.; Giugliano, R.P.; Park, J.G.; Ruzza, A.; Sever, P.S.; Keech, A.C.; Sabatine, M.S. Cardiovascular Benefit of Lowering Low-Density Lipoprotein Cholesterol Below 40 mg/dL. Circulation 2021, 144, 1732–1734.
14. Sampson, U.K.; Fazio, S.; Linton, M.F. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: The evidence, etiology, and therapeutic challenges. Curr. Atheroscler. Rep. 2012, 14, 1–10.
15. Dhindsa, D.S.; Sandesara, P.B.; Shapiro, M.D.; Wong, N.D. The Evolving Understanding and Approach to Residual Cardiovascular Risk Management. Front. Cardiovasc. Med. 2020, 7, 88.
16. Nosrati, M.; Safari, M.; Alizadeh, A.; Ahmadi, M.; Mahrooz, A. The Atherogenic Index Log (Triglyceride/HDL-Cholesterol) as a Biomarker to Identify Type 2 Diabetes Patients with Poor Glycemic Control. Int. J. Prev. Med. 2021, 12, 160.
17. Averna, M.; Stroes, E.; Ogura, M.; Postadzhiyan, A.; Cercek, M.; Calabrò, P.; Suppressa, P. How to assess and manage cardiovascular risk associated with lipid alterations beyond LDL. Atheroscler. Suppl. 2017, 26, 16–24.
18. Zhan, X.; Yang, M.; Zhou, R.; Wei, X.; Chen, Y.; Chen, Q. Triglyceride to high-density lipoprotein cholesterol ratio is associated with increased mortality in older patients on peritoneal dialysis. Lipids Health Dis. 2019, 18, 199.
19. Matsumoto, I.; Misaki, A.; Kurozumi, M.; Nanba, T.; Takagi, Y. Impact of nonfasting triglycerides/high-density lipoprotein cholesterol ratio on secondary prevention in patients treated with statins. J. Cardiol. 2018, 71, 10–15.
20. Grundy, S.M.; Brewer, H.B., Jr.; Cleeman, J.I.; Smith, S.C., Jr.; Lenfant, C.; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004, 109, 433–438.
21. Belete, R.; Ataro, Z.; Abdu, A.; Sheleme, M. Global prevalence of metabolic syndrome among patients with type I diabetes mellitus: A systematic review and meta-analysis. Diabetol. Metab. Syndr. 2021, 13, 25.
22. Rezapour, M.; Shahesmaeili, A.; Hossinzadeh, A.; Zahedi, R.; Najafipour, H.; Gozashti, M.H. Comparison of Lipid Ratios to Identify Metabolic Syndrome. Arch. Iran. Med. 2018, 21, 572–577.
23. Rinkuniene, E.; Butkute, E.; Puronaite, R.; Petrulioniene, Z.; Dzenkeviciute, V.; Kasiulevicius, V.; Laucevicius, A. Arterial function parameters in patients with metabolic syndrome and severe hypertriglyceridemia. J. Clin. Lipidol. 2017, 11, 901–907.
24. Nur Zati Iwani, A.K.; Jalaludin, M.Y.; Yahya, A.; Mansor, F.; Zain, F.; Hong, J.Y.H.; Wan Mohd Zin, R.M.; Mokhtar, A.H. TG: HDL-C Ratio as Insulin Resistance Marker for Metabolic Syndrome in Children With Obesity. Front. Endocrinol. 2022, 13, 852290.

25. McLaughlin, T.; Abbasi, F.; Cheal, K.; Chu, J.; Lamendola, C.; Reaven, G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann. Intern. Med. 2003, 139, 802–809.
26. Lelis, D.F.; Calzavara, J.V.S.; Santos, R.D.; Sposito, A.C.; Griep, R.H.; Barreto, S.M.; Molina, M.; Schmidt, M.I.; Duncan, B.B.; Bensenor, I.; et al. Reference values for the triglyceride to high-density lipoprotein ratio and its association with cardiometabolic diseases in a mixed adult population: The ELSA-Brasil study. J. Clin. Lipidol. 2021, 15, 699–711.
27. Abbasian, M.; Delvarianzadeh, M.; Ebrahimi, H.; Khosravi, F. Lipid ratio as a suitable tool to identify individuals with MetS risk: A case- control study. Diabetes Metab. Syndr. 2017, 11 (Suppl. S1), S15–S19.
28. Nie, G.; Hou, S.; Zhang, M.; Peng, W. High TG/HDL ratio suggests a higher risk of metabolic syndrome among an elderly Chinese population: A cross-sectional study. BMJ Open 2021, 11, e041519.
29. Shin, H.G.; Kim, Y.K.; Kim, Y.H.; Jung, Y.H.; Kang, H.C. The Relationship between the Triglyceride to High-Density Lipoprotein Cholesterol Ratio and Metabolic Syndrome. Korean J. Fam. Med. 2017, 38, 352–357.
30. Mardi, P.; Abdi, F.; Ehsani, A.; Seif, E.; Djalalinia, S.; Heshmati, J.; Shahrestanaki, E.; Gorabi, A.M.; Qorbani, M. Is non-high-density lipoprotein associated with metabolic syndrome? A systematic review and meta-analysis. Front. Endocrinol. 2022, 13, 957136.
31. Wakabayashi, I.; Daimon, T. Comparison of discrimination for cardio-metabolic risk by different cut-off values of the ratio of triglycerides to HDL cholesterol. Lipids Health Dis. 2019, 18, 156.
32. Gharipour, M.; Sadeghi, M.; Nezafati, P.; Dianatkhah, M.; Sarrafzadegan, N. Cardiovascular Disease Risk Assessment: Triglyceride/High-Density Lipoprotein versus Metabolic Syndrome Criteria. J. Res. Health Sci. 2019, 19, e00442.