JK SCIENCE

ORIGINAL ARTICLE

Usefulness of the TG/HDL Ratio in Predicting Cardiovascular Risk: A MMIMSR Experience

Sonu Kr Singh, Jyoti Aggarwal, Gobardhan Kathariya, Sajaad Manzoor*

Abstract

The present study was aimed to compare traditional lipid measures with the lipid ratios to establish a better marker for the assessment of coronary artery disease (CAD) risk. The comparison of traditional lipid parameters and lipid ratios were made in terms of independent 't' test, area under receiver operating characteristic (AUROC) curve and logistic regression analysis. LDL-C and HDL-C could not correlate well with CAD risk prediction. Strikingly, TG/HDL ratio was found to be more significantly associated in comparison to any of the individual lipid parameters as well as TC/HDL and LDL/HDL ratios when compared in terms of AUROC and logistic regression analysis, while LDL/HDL ratio could not correlate. Altogether, these findings infer that TG/HDL ratio is a better parameter in CAD risk prediction. Additionally, the TG/HDL ratio being calculated parameter incurs no additional cost to the patients and health care system. Henceforth, the authors suggest the incorporation of the TG/HDL ratio in the routine lipid panel for the better diagnosis and treatment of dyslipidemia.

Key Words

Coronary artery disease, Routine lipid profile, Lipid ratios, AUROC, Logistic regression analysis.

Introduction

Dyslipidemia has long been suspected to contribute in the pathogenesis of cardiovascular risk as reported by several studies (1,2). Recent epidemiologic studies have supported that the lipid ratios i.e. TC/HDL, TC/HDL, LDL/HDL, non-HDL/HDL, apo-A1/apo-B are superior than any of the individual lipid parameters as the predictor for coronary artery disease (CAD) risk (3-6). The lipid ratios comprehensively reflect the balance between the atherogenic and antiatherogenic potentials in individual.

In the present study, we have compared Total Cholesterol/High Density Lipoprotein (TC/HDL), Triglycerides/High Density lipoprotein (TG/HDL) and Low-Density Lipoprotein/High Density Lipoprotein (LDL/HDL) ratios for the assessment of CAD risk. The TG/HDL ratio was initially proposed by Gaziano *et al.* (7) and correlates inversely with the plasma level of small, dense LDL particles. Furthermore, the preliminary evidences suggest that TG/HDL ratio correlates well with severity of CAD (5, 6, 8). Therefore, this ratio has emerged as an attractive surrogate measure of atherogenicity of the plasma lipid profile. A TG/HDL ratio of < 2 is considered as normal.

The TC/HDL ratio, also known as Castelli Index (CI) is suggested to be an excellent predictor of CAD risk as proposed by Dr. William Castelli and suggested target for TC/HDL is < 4.5 (9). Recently, Zhu *et al*. reported that TC/HDL correlated well in CAD patients (10).

The LDL/HDL ratio appears to be as useful ratio as it reflects two-way traffic of cholesterol entering and leaving the arterial intima in a way that the individual levels of LDL and HDL do not. Thus, it is believed that the LDL/HDL ratio would correlate better with the CAD risk rather than LDL or HDL alone. Zhu *et al.* (10) also reported that LDL/HDL correlated well in CAD patients.

From the Department of Biochemistry and Cardiology*, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Haryana- India

Correspondence to: Dr. Jyoti Aggarwal, Professor, Department of Biochemistry, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Haryana.

The LDL/HDL ratio of less than 2 is considered as ideal.

Moreover, lipid ratios are calculated parameters and thus, incur no additional cost to healthcare system. In view of this fact as well as being a better parameter in prediction of CAD risk, is a need for incorporation of these parameters in routine lipid profile panel in India. Therefore, the present study was conducted to study the usefulness of these lipid ratios in evaluation of CAD risk.

Material and Methods

This is a case-control study involving the CAD patients attending Cardiology OPD in MM Super Speciality Hospital, Mullana, Ambala. Freshly diagnosed hypertensive and CAD patients aged between 20-60 years were included in this study along with 50 age and sex matched healthy individuals as control. Patients of Diabetes mellitus, Kidney disorders, Liver diseases as well as patients on follow up/extensive medical treatment/ lipid lowering drugs were excluded. The study was duly approved by institutional ethical committee.

After the collection of blood sample, serum total cholesterol (TC), triglycerides (TG), HDL were estimated by Simens Dimensions RxL in the clinical biochemistry lab, Department of biochemistry, MMIMSR. LDL and VLDL were calculated by Friedwald Formula and further lipid ratios i.e. TG/HDL, TC/HDL and LDL/HDL were calculated.

Detailed history of the patient's including history of alcohol, smoking, diet (vegetarian and non-vegetarian), medications, family history of diabetes mellitus/ hypertension was recorded. After generation of data it was compiled, tabulated and statistical analysis was performed using SPSS 22 version. The independent student 't' test was used to compare the means of various blood parameters (TC, TG, HDL, LDL, VLDL, TC/HDL, TG/HDL and LDL/HDL) between the study and control groups. ROC analysis was done to compare the predictive values of lipid ratios and further Logistic regression analysis was done to determine regression coefficient in hypertriglyceridemic individuals. The area under ROC is considered a global performance indicator for a prognostic factor (11). Greater area under curve of the ROC curve indicated better markers of the study. A significant level in the data was considered only at $p < 0.05$.

Results

Among the 150 individuals who had participated in the study, males and females constituted 62%, 38% respectively and male/female ratio was 1.6 .The age-wise distribution of the subjects demonstrated that distribution of subjects were 18.7%, 21.3%, 33.3% and 26.7% in the age groups 20-30, 30-40, 40-50 and 50-60 years respectively. The blood pressure of less than 120/ 80 mm/Hg to 130/90 mm/Hg was considered normal.

Serum TC, TG, HDL, LDL, VLDL was measured while TC/HDL, TG/HDL and LDL/HDL ratios were calculated for all the subjects. The results of TC/HDL, TG, HDL and LDL/HDL ratios are illustrated in *Table 1***.**

To compare the predictive values of individual lipid markers as well as lipid ratios, ROC curve analysis was done. Analysis of ROC showed that only TG/HDL ratio (0.892 at 95% Confidence Interval: 0.842, 0.942) and TC/HDL ratio (0.750 at 95% Confidence Interval: 0.674, 0.827) were more useful for predicting CAD risk with former showing more strong association *(Figure 1)*.

Further, to compare the predictive values of TC/HDL and TG/HDL ratios in terms of hypertriglyceridemia, patients were divided into 2 groups; Group A (serum TG > 200 mg/dl) and Group B (serum TG ≤ 200 mg/dl). On comparison the results were more significant for TG/ HDL ratio in comparison to TC/HDL ratio *(Table 2)*.

Logistic regression analysis *(Table 3)* and combined ROC *(Figure 2)* were further done. The regression coefficient (B) was found to be -0.711 for TC/HDL ratio indicating the negative association with respect to the serum Triglyceride levels (TG) while it was 1.329 for

Table 1: Comparison of TC/HDL, TG/ HDL, LDL/HDL Ratios in Control and Test Group

Lipid Ratios	Group	N	Mean ± S. D	*t*-value	*p*-value
TC/HDL	Control	50	3.90 ± 0.71	4.647	.0001**
	Test	100	5.16 ± 1.85		
TG/HDL	Control	50	2.58 ± 0.76	7.367	.0001**
	Test	100	5.89 ± 3.13		
LDL/HDL	Control	50	2.38 ± 0.61	2.604	.010*
	Test	100	2.96 ± 1.51		

The data was expressed as mean ± SD. N denotes number of subjects. The significance was determined by independent student 't' test using SPSS 22 version. $p < 0.05$ was considered as significant *, $p < 0.001$was considered as highly significant**

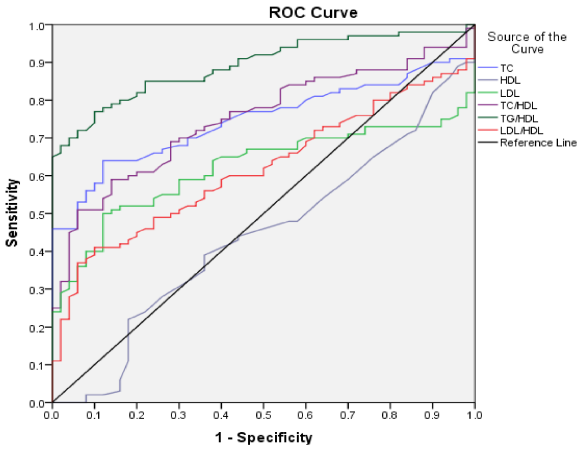

Figure 1: Receiver Operating Characteristic Curve for TC, LDL, HDL and Lipid Ratios

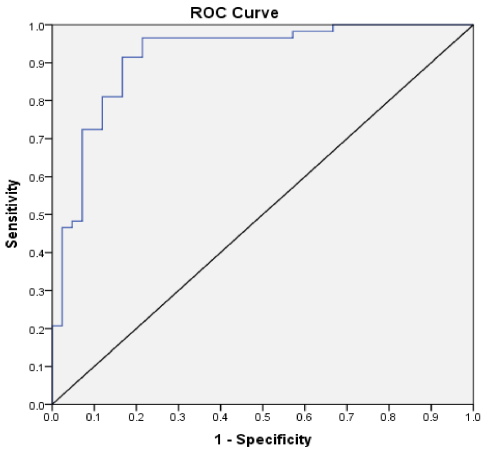

Figure 2: Combined ROC Curve for TC/HDL and TG/HDL Ratios.

Table 2: Comparison of TC/HDL and TG/HDL Ratios in Group A (Serum Triglycerides >200 mg/dl) and Group B (Serum Triglycerides ≤ 200 mg/dl)

Parameter	Group	N	Mean ± SD	*t*-value	*p*-value
TC/HDL	A (>200)	58	5.56 ±1.87	2.653	.009*
	B (≤200)	42	4.60 ± 1.87		
TG/HDL	A (>200)	58	7.42 ± 2.99	6.956	.0001**
	B (≤200)	42	3.79± 1.86		

The data was expressed as mean ± SD. N denotes number of subjects. The significance was determined by independent student '*t*' test using SPSS 22 version. $p < 0.05$ was considered as significant*, $p < 0.001$was considered as highly significant**.

Table 3: Regression Coefficient Analysis of the Independent Variables (TC/HDL and TG/HDL) with Dependent Variables (TG >200 and TG ≤ 200)

Independent Variables	Regression Coefficient	Standard error	Wald	Df	*p*-value	Odd-Ratio	95% C.I. for OR	
							Lower	Upper
TC/HDL	-.711	.281	6.421	1	.011*	.491	.283	.851
TG/HDL	1.329	.280	22.469	1	.0001**	3.777	2.180	6.544
Constant	-2.973	1.085	7.503	1	.006*	.051		

$p < 0.05$ was considered as significant*, $p < 0.001$was considered as highly significant**.

TG/HDL ratio indicating the positive association. According to Omnibus tests (Chi-Square=59.84, p-value=.0001) of model coefficients, p-value is < 0.01 suggest that the procedure of logistic regression is appropriate. The Wald test clearly shows that there are significant variables (or predictors) namely TC/HDL and TG/HDL, which can predict the TG (>200) cases risk and following logistic regression equation, were obtained for the same *(Table 3)*. Coefficient of determination (R^2) was computed to check the association of variables in the current model. It is evident from Cox & Snell R^2= 0.45 and Nagelkerke's R^2 = 0.606 value that there is a strong association of selected independent variables (TC/HDL and TG/HDL) with dependent variables (TG >200 and TG ≤ 200) (Cox & Snell,1989 and Nagelkerke, 1991) (12,13).

Figure 2 offers an excellent visual performance of the model, based on two predictors. The receiver operating characteristic (ROC) curve and the area under the curve (AUC = 91.6%) suggest that the model works very well

with minimum standard error of 0.030 and with a close range of 95% confidence intervals (CI 0.857–0.975). If the area under the ROC curve approach is unity, it means the efficiency of the TG cases is very high (14). In the present study the area

under the ROC curve is 0.916 indicating that one can differentiate between TG (>200) case and TG (≤ 200) with high accuracy, based on the two predictors.

Discussion

Notwithstanding, cardiovascular diseases are the multifactorial processes. Strikingly, lipoprotein metabolism is one the key factor which represents around 50% of the population associated with predisposition of CAD (15). It has been commonly argued that lipid ratios may be an acceptable alternative for identifying the CAD risk (16,17). Moreover, there is a paucity of information regarding the implications of the lipid ratios in CAD risk prediction.

On comparing the lipid ratios in terms of AUROC; it was found that the ratio of LDL/HDL could not demonstrate a good correlation (0.617 at 95% confidence interval: 0.529, 0.705) with CAD risk prediction while the TC/HDL ratio was significantly associated (0.750 at 95% confidence interval: 0.674, 0.827). It could possibly be associated with the excess levels of cholesterol fraction in the plasma lipid; however, two-third of plasma cholesterol are found in LDL, consequently TC/HDL ratio was more significant (18).

It is noteworthy here that in our study TG/HDL ratio was found to be more significantly associated with CAD risk prediction as compared to other lipid ratios. These findings are consistent with the studies carried out by Ain *et al.* (19), Du *et al.* (20) and Protasio Lemos da Luz *et al.* (6). Interestingly, these authors also compared the lipid ratios in terms of student 't' test, AUROC analysis, logistic regression analysis and found TG/HDL ratio to be more significantly associated. Additionally, a high TG/HDL ratio could be a risk factor for the prevalence of SBI (Silent Brain Infarct) lesions in a neurologically healthy population (21). Thus, TG/HDL ratio has been found to be of great clinical significance in prediction of lipid related abnormalities even beyond LDL-C in account of the studies conducted by Nam *et al.* (21) and Hajian Tilaki *et al.* (22).

Further in this study, the ratios of TC/HDL and TG/HDL were compared in terms of triglycerides levels, combined ROC as well as Logistic regression analysis to find out the superiority of one over the other. TG/HDL ratio was again found to be more pronounced to that of TC/HDL ratio, thus further supporting the implication of this ratio in CAD risk prediction.

Conclusion

In present study, TG/HDL ratio was found to be an early and better parameter in the CAD risk prediction. Owing to a calculated parameter, it does not incur any additional cost to the patients and health care system. Therefore, it is an easy as well as accessible measure in recognizing the individuals who are at higher risk of developing CAD. Henceforth, the authors suggest the incorporation of the TG/HDL ratio in the routine lipid panel for the better diagnosis and treatment of dyslipidemia.

Acknowledgement

The authors are thankful to Department of Biochemistry and Department of Cardiology, MMIMSR, Mullana, Ambala for providing the research facilities and highly appreciate Dr. Rajendra Prasad, Professor, Biochemistry, MMIMSR (Ex-Professor and Head, Biochemistry Department, PGIMER, Chandigarh) for critically reviewing the manuscript. The authors would also like to acknowledge and thanks Mr. Rajesh for his assistance in statistical analysis.

References

1. American Heart Association. Cholesterol statistics. Available at: http://www.Americanheart.org. Accessed 10 / 02/2020.
2. World health Organization. Quantifying selected major risk to health. In: The world health report 2002- reducing risk, promoting healthy life. Chapter 4. Geneva: World Health Organization; 2002. p 47-97.
3. Siniawski D, Massonm W, Sorroche P, Casañas L, Krauss J, Cagide A. Correlation between Apolipoprotein B-to-Apolipoprotein A1 Ratio and Total-to-HDL-Cholesterol Ratio in a Healthy Population: Should Castelli Index be Updated? *Rev Argent Cardiol* 2011;79:33-38.
4. Panimathi R, Rekha K, Geetha K. Total cholesterol/HDL ratio - An individual predictor of atherosclerosis in acute coronary syndrome. *Sch J App Med Sci* 2017;5(8C):3204-08.
5. Kohli A, Siddhu A, Pandey RM, Reddy KS. Relevance of the triglyceride-to-high-density lipoprotein cholesterol ratio as an important lipid fraction in apparently healthy, young, and middle-aged Indian men. *Indian J Endocrinol Metab* 2017;21(1):113–18.

6. Lemos da Luz P, Favarato D, Faria-Neto JR Jr, Lemos P, Chagas AC. High ratio of triglycerides to HDL-cholesterol predicts extensive coronary disease. *Clinics* 2008;63(4):427-32.

7. Gaziano JM, Hennekens, CH, O'Donnell CJ, Breslow JL, Buring JE: Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. *Circulation* 1997;96:2520-25.

8. Wen JH, Zhong YY, Wen ZG, Kuang CQ, Liao JR, Chen LH, *et al.* Triglyceride to HDL-C ratio and increased arterial stiffness in apparently healthy individuals. *Int J Clin Exp Med* 2015;8(3):4342-48.

9. Millán J, Pintó X, Muñoz A, Zúñiga M, Rubiés-Prat J, Pallardo LF, Masana L*et al*. Lipoprotein ratios: Physiological significance and clinical usefulness in cardiovascular prevention. *Vasc Health Risk Manag*.2009;5:757-65..

10. Zhu L, Lu Z, Zhu L, Ouyang X, Yang Y, He W*et al*. Lipoprotein ratios are better than conventional lipid parameters in predicting coronary heart disease in Chinese Han people. *Kardiol Pol* 2015;73(10):931-38

11. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. *Prev Vet Med* 2000 30;45(1-2):23-41.

12. Cox DR, Snell EJ. The analysis of binary data. 2nd ed. London: Chapman and Hall; 1989

13. Nagelkerke NJD. A note on a general definition of the coefficient of determination. *Biometrica* 1991;78(3):691-92.

14. Balaswamy S, Vardhan RV. Confidence interval estimation of an ROC curve: An application of Generalized Half Normal and Weibull Distributions. *J Probab Stat* 2015:934362. doi:10.1155/2015/934362

15. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364(9438):937-52.

16. Wang TD, Chen WJ, Chien KL, Seh-Yi Su SS, Hsu HC, Chen MF*et al.* Efficacy of cholesterol levels and ratios in predicting future coronary heart disease in a Chinese population. *Am J Cardiol* 2001 1;88(7):737-43.

17. McQueen MJ, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J *et al*. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet* 2008 19;372(9634):224-33.

18. Ascaso J, González Santos P, Hernández Mijares A, et al. Management of dyslipidemia in the metabolic syndrome. Recommendations of the Spanish HDL Forum. *Am J Cardiovasc Drugs* 2007;7:39-58.

19. Ain QU, Asif N, Gilani M, Noreen, Sheikh W, Akram A. To determine cut off value of triglycerides to HDL ratio in cardio vascular risk factors. *Biochem Anal Biochem* 2018; 7(2):1000354.

20. Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovasc Diabetol* 2014;13:146.

21. Nam KW, Kwon HM, Jeong HY, Park JH, Kwon H, Jeong SM. High triglyceride/HDL cholesterol ratio is associated with silent brain infarcts in a healthy population. *BMC Neurology*. 2019; 19:147.

22. Hajian-Tilaki K, Heidari B, Bakhtiari A. Triglyceride to high-density lipoprotein cholesterol and low-density lipoprotein cholestrol to high-density lipoprotein cholesterol ratios are predictors of cardiovascular risk in Iranian adults: Evidence from a population-based cross-sectional study. *Caspian J Intern Med.* 2020;11(1):53-61.