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Journal of Cardiac Disorders and Therapy

RESEARCH ARTICLE

ISSN: 2637-465X

Cholesterol / HDL Ratio Categories and Estimated Coronary Artery Disease Risk

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Citation: Zinat Nadia Hatmi, Mitra Mahdavi-Mazdeh, Seyed Saeid Hashemi-Nazari, Ebrahim Hajighasemi (2024) Cholesterol / HDL Ratio Categories and Estimated Coronary Artery Disease Risk, J Cardiac Disord and Ther 5: 102

Abstract

Background: Total cholesterol to HDL- Cholesterol ratio (TC/HDL-C) has been recommended as a strong predictor of future cardiovascular events. There is no previous report on the relationship between lipid ratios and their subgroups with other coronary artery disease (CAD) risk factors.

Materials and Methods: A large scale cohort study of 31999 initially healthy people was conducted. Standardized methods for detection of CAD risk factors were used. Statistical tests of independent sample T-Test, ANOVA and Pearson correlation coefficient and linear regression was conducted to evaluate the relationships.

Results: 51.4 percent of the study population is at moderate risk category, 13.8 percent in low risk, 13.6 % in very low risk and 0.4 % in high risk category of future ischemic heart attack according to the ratio of TC/HDL-C. Multivariate adjusted parameter estimation revealed a statistically significant increase in the ratio of TC/HDL-C based on every unit increment in TG> 200 Mg/dl, TC> 170Mg/dl, LDL-C alone, systolic blood pressure and cigarette smoking status.

Conclusions: Multivariate adjusted relationship between ratio of TC/HDL-C and CAD risk factors revealed that, one unite increase in TG> 200 Mg/dl, total cholesterol> 170 Mg/dl, LDL-C, systolic blood pressure will tend to significantly increment in the quantity of TC/HDL-C ratio. We observed that smoking habit significantly increased the quantity of this ratio.

Keywords: Coronary Artery Disease; Lipid Ratios; Prediction; Prevention; Risk Stratification; Risk Modification

Introduction

Total cholesterol to HDL- Cholesterol (HDL-C) ratio (TC/HDL-C) has been recommended as a strong predictor of future cardiovascular events [1, 2]. The adjusted hazard ratio of cardiovascular events among individual with highest level of TC/HDL-C ratio was calculated about four[1]. This lipid ratio was estimated to be as strong as the ratio of Apo lipoprotein B100/ Apo lipoprotein A-I to predict future cardiovascular events[1].

Cardiovascular disease (CVD) yet considered as a worldwide pandemic which trended toward worsening with the emergence of COVID-19 pandemic. The most recent heart disease and risk factors statistics provided by American heart association (AHA) and national institute of health (NIH) on April, 2024 report total CVD prevalence 48.6% involving 127.9 million US adults over 20 years . Lifetime risk CVD varied between 15.3%-38.6% in females of 55-85 years and 21.5%-47.7% in males. CVD are responsible for 40.3% of mortalities in US population and considered as the leading cause of death globally. Direct and indirect cost of CVD estimated as 252.2 billion US dollars annually.

The simply conducted ratio of TC/HDL-C has been demonstrated to be superior to the measurement of total cholesterol and LDL-C alone [3]. Based on the hypothesis that inflammatory status [4] and dyslipidemia [1] play a crucial role in pathopoiesis [5] of atherosclerotic coronary artery disease (CAD) and stroke [6], and patients oriented evidences that support the regression of atherosclerotic lesions after treatment of high LDL-C and low HDL-C level [7] associated with significant decline in future clinical outcomes and hazard of clinical coronary events, it is concluded that regular monitoring of the lipoproteins and lipid ratios can guide efficacious and more precise designing of both primary [8, 9] and secondary prevention strategies [10-13, 14].

In primary prevention and clinical practice, measurement of total cholesterol/ HDL-C ratio is superior to the evaluation of Apo B and Apo A-I [15]. To our search strategy there was not previous report on the relationship between lipid ratios and their categories with other CAD risk factors. Therefore, we designed to investigate the relationships between TC/HDL-C ratio and CAD risk factors in a large population based research in 31999 initially healthy adults. Determination of new features of the relationship between CAD risk factors might be implicated to improve prevention guidelines [8, 9] and reclassification of CAD hazard [16]. It has been shown that mean level of total cholesterol in population was declined as a consequence of the national risk modification efforts [17] and appropriate management [18].

Materials and Methods

Study design, study population and risk factor assessments: Details of present large scale study of MSTDT among 31999 initially healthy people, and standardized methods for detection of CAD risk factors were described in a prior published article [19].

31999 initially healthy people were recruited to the study from ten medical clinics in the capital city. Adult above 18 years with no history of previous CVD underwent clinical examination and para-clinical tests. CAD risk factors assessment conducted with standardized method [19]. Individuals with past medical history of documented CAD and who were reluctant to conduct the lab tests were excluded.

Statistical analysis: Statistical analysis conducted use SPSS V22 computer package. Data from 31999 was described by calculating mean ± (SD) and frequencies. Uni variable analysis: statistical tests of independent sample T-Test, ANOVA and Pearson correlation coefficient were conducted to evaluate relationship between TC/HDL-C ratio and different CAD risk factors.

Multivariate analysis: linear regression was conducted to evaluate adjusted parameter estimation of relationship between TC/HDL-C ratio and well known CAD risk factors.

Statistical relations were considered significant at $p< 0.05$.

Results

Mean and SD of TC/HDL-C ratio for 31999 study participants was 4.70 ± (1.25). Mean and SD of LDL-C / HDL-C ratio and Triglyceride / HDL-C ratio, were 2.84 ± (1.00) and 4.40 ± (2.72) respectively.

Table 1 demonstrates the distribution of TC/HDL-C ratio across different categories of CAD risk factors comprising age, gender, blood pressure categories, LDL-C, and BMI.

Aside from gender and diastolic blood pressure, uni variable relationship between the ratio of TC/HDL-C and CAD risk factors of smoking status, systolic blood pressure, fasting blood sugar, triglyceride, LDL-C, body mass index (BMI) and age were statistically significant (P< 0.05).

Table 1: Distribution of TC/HDL-C ratio across subgroups of CAD risk factors in 31999 initially healthy individuals

Factors		Mean ± SD of TC/HDL-C ratio	Significance level
Gender	Female	4.65 ± 1.26	0.33
	Male	4.70 ± 1.24	
Smoking	Yes	4.51 ± 1.16	0.001
	No	4.28 ± 0.97	
Systolic blood pressure (SBP)	Over 140 mmHg	4.58 ± 1.07	0.001
	Under 40mmHg	4.71 ± 1.25	
Diastolic blood pressure (DBP)	Over 90 mmHg	4.69 ± 1.15	0.81
	Under 90 mmHg	4.71 ± 1.25	
SBP	Under120mmHg	4.69 ± 1.21	0.001
	Over 120 mmHg	4.78 ± 1.37	
DBP	Under 80 mmHg	4.68 ± 1.48	0.20
	Over 80 mmHg	4.71 ± 1.21	
Fasting blood sugar	Over 126 Mg/dl	4.92 ± 1.37	0.001
	Under 126 Mg/dl	4.69 ± 1.23	
Triglyceride	Over 200 Mg/dl	5.38 ± 1.48	0.001
	Under 200 Mg/dl	4.53 ± 1.10	
LDL-C	Under 130 Mg/dl	5.57 ± 1.34	0.001
	Over 130 Mg/dl	4.41 ± 1.00	
BMI	< 18.5	4.17 ± 1.11	0.001
	18.5 – 24.9	4.64 ± 1.22	
	25-29.9	4.90 ± 1.24	
	30-39.9	4.94 ± 1.38	
	≥ 40	4.74 ± 1.13	
Age groups	Under 30	4.40 ± 1.17	0.001
	30-40 year	4.71 ± 1.31	

	40-50 year	4.79 ± 1.25	
	50-60 year	4.78 ± 1.20	
	Over 60 year	4.69 ± 1.13	

*SBP = Systolic blood pressure, † DBP= Diastolic blood pressure, ‡Mg/dl=Milligram per deciliter

§MmHg =Millimeter of Hg, "HDL-c=High density lipoprotein, ¶LDL-c=Low density lipoprotein

#TC=total cholesterol, *SD=standard deviation, †BMI=body mass index, ‡ CAD=coronary artery disease

Pearson correlation coefficients between TC/HDL-C ratio and well know CAD risk factors were presented in table 2. Strong correlations detected between LDL-C / HDL-C ratio (r= 0.902 P= 0.001) and TC/HDL- C ratio. Moderate correlations were found between TC/HDL-C ratio and triglyceride / HDL-C ratio (r= 0.578 P = 0.001), LDL-C (r=0.543 p= 0.001) and triglyceride (r= 0.368 p= 0.001). Weak Pearson correlations were observed between the ratio of TC/HDL-C and BMI (r= 0.118 P= 0.001), Age (r= 0.068 P= 0001) and fasting blood glucose (r= 0.053 P= 0.001).

Table 2: Pearson correlation coefficients between the ratio of TC/HDL-C and CAD risk factors in 31999 initially healthy individuals

TC/HDL-C ratio with coronary artery disease risk factors	Pearson R	Significance level
Fasting blood sugar	0.053	0.001
LDL-C	0.543	0.001
Triglyceride	0.368	0.001
Age	0.068	0.001
Body mass index	0.118	0.001
LDL-C/HDL-C ratio	0.902	0.001
Triglyceride/HDL-C ratio	0.578	0.001

* HDL-c=High density lipoprotein, †LDL-c=Low density lipoprotein, ‡TC=total cholesterol, §CAD=coronary artery disease

The ratio of TC/HDL-C also treated as categorical variable. Refer to national cholesterol education program [9, 20] classification of TC/HDL-C ratio including: very low risk < 3.4, low risk 4.0, average risk 5.0, moderate risk 9.5 and high risk > 23 for male and < 3.3, 3.8, 4.5, 7.0 and over 11 respectively for female. Accordingly, the results of Pearson chi-square test and likelihood ratios of relationship between different categories of TC/HDL-C ratio and the other CAD risk factors in male gender appear in table 3.

Distribution of TC/HDL-C ratio in 24863 male participants in this research revealed that: frequency of very low risk, low risk, average risk, moderate risk and high risk was 13.6 %, 13.8 %, 39.9 %, 32.3 % and 0.4% respectively. We found statistically significant linear by linear association between the ratio of TC/HDL-C with LDL-C> 130 mg/dl 2921.14 (p= 0.001), BMI categories of overweight and obesity 268.05 (P= 0.001).

Pattern of TC/HDL-C ratio among female participants (n= 459) demonstrated the prevalence of 16.8 percent of very low risk, 12.6 % of low risk, 19.2 % of average risk, 51.4 % of moderate risk and 0 % of high risk.

Table 4 is shown the comparison of different CAD risk factor across five levels of TC/HDL- C ratio. We observed a statistically significant relationship between the LDL-C> 130 mg/dl, five groups of BMI and different age, with a greater likelihood ratio (58.77) for LDL-C> 130 Mg/dl.

Table 3: Relationship between different categories of TC/HDL-C ratio and CAD risk factors in men

Five categories of TC/HDL-C ratio with coronary artery disease risk factors	Significance level of X^2 test	Likelihood ratios	Significance level for likelihood ratios
Diastolic blood pressure>80mmHg	0.001	37.57	0.001
LDL-C>130 Mg/dl	0.001	3575.54	0.001
Systolic blood pressure>120 mmHg	0.001	24.57	0.001
Fasting blood sugar > 126 Mg/dl	0.001	52.45	0.001
Systolic blood pressure>140 mmHg	0.001	22.09	0.001
Diastolic blood pressure> 90mmHg	0.001	20.72	0.001
Five groups of BMI	0.001	376.94	0.001
Smoking status	0.001	107.90	0.001
Five groups of age	0.001	309.69	0.001

*Mg/dl=Milligram per deciliter, †MmHg =Millimeter of Hg,‡ HDL-c=High density lipoprotein,§ LDL-c=Low density lipoprotein, "TC=total cholesterol, ¶BMI=body mass index, # CAD=coronary artery disease

Table 4: Relationship between different categories of TC-HDL-C ratio and CAD risk factors in females

Five categories of TC/HDL-C ratio with coronary artery disease risk factors	Significance level of X^2 test	Likelihood ratios	Significance level of likelihood ratios
Diastolic blood pressure> 80 mmHg	0.11	6.42	0.09
Five groups of age	0.014	25.69	0.012
LDL-C > 130 Mg/dl	0.001	58.77	0.001
Systolic blood pressure> 120 mmHg	0.89	0.59	0.89
Fasting blood sugar>126 Mg/dl	0.26	6.48	0.09
Systolic blood pressure> 140mmHg	0.81	1.33	0.72
Five categories of BMI	0.051	21.03	0.05

* Mg/dl=Milligram per deciliter, †MmHg =Millimeter of Hg, ‡HDL-c=High density lipoprotein,§ LDL-c=Low density lipoprotein, "TC=total cholesterol, ¶BMI=body mass index, # CAD=coronary artery disease

Furthermore, there was a significant linear trend between the ratio TC/HDL-C by LDL-C> 130 Mg/dl (43.32 P= 0.001), and five groups of BMI (7.26 P= 0.007) in women. These trends could be translated as the fact that, the ratio of TC/HDL-C increases with increment of BMI and amount of LDL-C (over 130 Mg/dl)

Multivariable Analysis:

In order to estimate multivariable adjusted relations between different CAD risk factors and categories of TC/HDL-C ratio, we conducted a polynomial regression model.

Fully adjusted Odds Ratio was calculated and demonstrated in table 5. These parameters estimation revealed that every unit increment in the level of risk factors including: TG> 200 Mg/dl, total cholesterol> 170 Mg/dl, LDL- C, systolic blood pressure and smoking status leads to a statistically significant increase in quantity of TC/HDL-C ratio.

Odds ratios are adjusted for: FBS, age groups, BMI, and gender.

Table 5: Fully adjusted polynomial regression model of relationship between five categories of TC/HDL-C ration and well known coronary artery disease risk factors

Parameters	Beta	Significance level
Triglyceride> 200 Mg/dl	0.036	0.001
Total cholesterol> 170 Mg/dl	0.030	0.001
LDL-C Mg/dl	0.025	0.001
Systolic blood pressure mmHg	0.022	0.001
Smoking status	0.015	0.001

* Mg/dl=Milligram per deciliter, †MmHg =Millimeter of Hg, ‡LDL-c=Low density lipoprotein , TC= Total cholesterol, HDL= High density lipoprotein

Discussion

Multivariable adjusted relationship between ratio of TC/HDL-C and CAD risk factors revealed that, one unite increase in TG> 200 Mg/dl, total cholesterol> 170 Mg/dl, LDL-C, systolic blood pressure will tend to significantly increment in the quantity of TC/HDL-C ratio. Moreover we observed that smoking habit strongly increased the quantity of this ratio. Study of Lipid measures and CAD risk factors in women [1, 21] demonstrated that the Apo lipoprotein B l00/ Apo lipoprotein A1 ratio has not preference to the ratio of TC/HDL-C. Thus, data from this large scale cohort study proved that, feasibly conducted ratio of TC/HDL-C has the ability to predict cardio vascular events as equal as Apo lipoprotein fractions[1].

We found that 51.4 percent of the study population are at moderate risk category of TC/HDL-C ratio. Accordingly, about half of our initially healthy individuals are at moderate risk for future cardiovascular events.

Our findings revealed that the highest correlation coefficient was observed between the ratio of TC/HDL-C and ratio of LDL-C/HDL-C, triglyceride/ HDL-C, LDL-C alone and triglyceride alone, respectively. On the other hand these findings are in accordance with those of previous researches, do recommend that the implication of such a lipid ratios[22, 23] are superior to the conduction of lipid profiles alone[1].

Correlation coefficient between the ratio of TC/HDL-C and fasting blood sugar (Mg/dl) was weak. However when we treated these variables as categorical factors the likelihood ratio (LR) of relationship between fasting blood glucose> 126 Mg/dl across five categories of TC/HDL-C ratio was 52.45 (P=0.001) in men. We believe these results demonstrated that, the amount of FBS over 126 Mg/dl might be in relation with different categories of TC/HDL-C ratio.

Relationship between the ratios of TC/HDL-C with different CAD risk factors revealed a different pattern among two sexes. Our data demonstrated a statistically significant relation between the ratio of TC/HDL-C with LDL-C > 130 Mg/dl, age groups and five groups of BMI in female individuals. However all the nine factors in table 3 were significantly in relation with the ratio in male. This variation may be associated with alterations in metabolism and insulin resistance syndrome among two different genders. The Quebec cardiovascular study in men [2] revealed that the ratio of TC/HDL-C is superior to LDL-C/HDL-C ratio in the prediction of ischemic heart disease risk, which endorse use of the strongest prognostic ratio of TC/HDL-C [1, 2, 24].

Reduction of this ratio in initially healthy individuals proved to be predictive of decline in risk of first ischemic heart attack [25]. Moreover the importance of TC/HDL-C ratio could be explained as a cumulative index of the existence of an atherogenic dyslipidemia disorder[19, 26] in companionship with insulin resistance [2]. This ratio is a marker of a group of metabolic abnormalities which could be detected in individuals with dyslipidemia of high TG and low HDL-C level. This type of dyslipidemia found to be associated with insulin resistance and abdominal obesity[2].

The ratio of TC/HDL-C introduced as atherogenic or Castelli index is the most practical vascular risk indicator with high predictive value. Practical implications of TC/HDL-C ratio can be describe in risk detection, risk stratification and risk modification of CVD.

Total cholesterol including LDL-C carries about 60 percent of plasma cholesterol. Numerator of the ratio comprises atherogenic lipid marker and the denominator has encompass atheroprotevtive lipid marker. Besides, HDL-C is associated with components of metabolic syndrome. At the presence of hypertriglyceridemia it is recommended to use TC/HDL-C ratio to detect dyslipidemia. Moreover, TC/HDL-C ratio has a great predictive power to detect carotid intima media thickness. Therefore we can implicate the ratio as major vascular risk predictor to estimate future cardiovascular events [27].

The TC/HDL-C ratio comprises HDL-C with atherosclerotic plaque regression capacity. Therefore, in risk modification of CVD it can be used as an estimator of treatment goal with a high predictive value [27].

We believe that the ratio of TC/HDL-C associated with inflammatory markers like high sensitive C-reactive protein could be considered as the most powerful estimator of cardiovascular risk.

Limitations and strength: limitations of our study are including: measurement of lipid profile and glucose just once. Besides, our data does not include measurement of inflammatory markers.

Merits of our study can be mentioned as: a large scale population based data in both women and men who were initially free of CAD symptoms. Also we evaluated CAD risk factors based upon standardized uniform method in whole study population.

Conclusion

51.4 percent of our study population is at moderate risk category, 13.8 percent in low risk, 13.6 % in very low risk and 0.4 % in high risk category of future ischemic heart attack according to the ratio of TC/HDL-C. Multivariate adjusted parameter estimation revealed a statistically significant increase in the ratio of TC/HDL-C based on every unit increment in TG> 200 Mg/dl, TC> 170Mg/dl, LDL-C alone, systolic blood pressure and cigarette smoking.

Acknowledgement

This study was supported by a grant from Tehran Municipality Health Center.

Ethical Issues

This study was reviewed and approved by the Tehran municipality health committee. Verbal consent was gathered from the eligible participants.

Funding

This research was supported by a grant from the Tehran municipality Health center.

Conflict of Interest

The authors declare that there is no conflict of interest.

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