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The Relationship Between Premature Myocardial Infarction with TC/HDL-C Ratio Subgroups in a Multiple Risk Factor Model

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Abstract

Introduction: So far, there is no evidence available to demonstrate the relationship between five subgroups of total cholesterol/high density lipoprotein cholesterol (TC/HDL-C) ratio with premature myocardial infarction (MI).

Objective: We conducted a case control study to probe more features of the relation between TC/HDL-C ratio and the five subgroups of the ratio with myocardial infarction under 55 years and above it.

Method: A hospital based case control study with incident cases was designed. Cases and controls were comprised of 523 under 55-year and 699 above 55-year documented newly diagnosed MI cases, respectively. Standardized clinical and para clinical method were used to ascertain disease and risk factors. Independent sample t-test, Pearson chi square test, Odds ratios and Mantel-Haenszel test and logistic regression analysis conducted to evaluate relationships.

Results: This study enrolled 1222 MI cases. Patients with very low risk category of TC/HDL-C ratio estimated OR=0.18 with 95% confidence interval (CI) (0.04-0.72) for developing MI under 55 years. Patients who had low risk category of TC/HDL-C ratio having OR=0.26 95% CI (0.07-0.89). Low risk and very low risk categories of the TC/HDL-C ratio compare to high risk subgroup of the ratio demonstrate decreased risk of developing MI under 55 years $p<0.05$.

Conclusion: Our study results can be translated as an aggressive treatment for lowering TC/HDL-C ratio in both general population and victims of coronary events. Mitigation of the level of TC/HDL-C ratio from low risk to very low risk category will attenuate the risk of MI under55 years about 8% which is the immediate clinical implication of our findings.

Key words: Algorithms; Coronary Artery Disease; Lipids; Myocardial Infarction; Risk

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INTRODUCTION

The ratio of total cholesterol/ high density lipoprotein cholesterol (TC/HDL-C) proved to be a strong predictor of future cardiovascular events (1, 2). It has been shown that the combination of the TC/HDL-C ratio associated with elevated high sensitive C-reactive protein (Hs-CRP) encompass higher predictive value for future cardiovascular events (3). Conventional and novel risk factors pattern of coronary artery disease (CAD) revealed a significant differences among younger individuals and the older patients, men and women, symptomatic and asymptomatic individuals and pre and post- menopausal status in women (4-8).

Variation in the TC/HDL-C ratio across different age groups has been found to be augmentative in both men and women (9). Investigation of the relationship between subgroups of TC/HDL-C ratio with premature cardiovascular events might be associated with illumination of the alterations exist in predictive metabolic indices for incidence of ischemic heart events. The ratio of TC/HDL-C may be a cumulative index of atherogenic dyslipoproteinemia (10). Elevation of the TC/HDL-C ratio beyond the level of average risk might be associated with attenuated risk for coronary events.

HDL-C level has been recognized as a protective lipid factor for occurrence of cardiovascular events in different populations (11). Yet measurement of this cardio protective lipid component associated with traditional lipid profiles has been

recommended by abundant recent evidences (1, 2, 5, 7). In order to tailor a global risk assessment model for secondary and primary prevention of CAD to dedicate precise preventive measures for both healthy individuals and patients with cardiovascular presentations we need to address the role of various CAD risk factors in a multiple risk factor combination. Such a multiple risk factor model treats the complexity of the relationship between risk factors or preventive factors with cardiovascular events. So, control measures which designed based on a global risk assessment method can guide more efficient and inclusive treatment strategies.

So far, there is no evidence available to demonstrate the relationship between five subgroups of TC/HDL-C ratio with premature coronary events. Therefore, we conducted a case control study to figure out more features of the relation between five subgroups of TC/HDL-C ratio with myocardial infarction under 55 years.

METHODS

Study design

This hospital-based case control study with incident cases was designed with adhering to STROBE criteria for observational studies. Study protocol was approved by the University review board (Ethics code: 20219-30-04). Verbal consent was obtained at the entry of the study.

Study population

Cases: were comprised of 523 documented first ever myocardial infarction (MI) patients who were under 55 years and randomly selected among MI cases admitted to teaching hospitals of the capital city.

Controls: Including 699 documented newly diagnosed cases of MI who were above 55 years and selected with simple random sampling among eligible controls.

Cases and controls have been matched on diastolic hypertension and body mass index.

Definition

In order to compare cases and controls based on different subgroups of the TC/HDL-C ratio, we divided TC/HDL-C ratio into 5 subgroups refer to the national cholesterol education program (NCEP) definition (12, 13). These 5 categories including: very low risk, low risk, average risk, moderate risk and high risk.

Risk factor detection

CAD risk factors of cases and controls were measured by taking medical history, physical examination, laboratory test including: fasting plasma sugar enzymatic ally, 12 hours over night fasting lipid profile using calorimetric method, and calculation of lipid ratios.

Statistical analysis

Independent sample t-test, Pearson chi square test, Odds ratios calculation and Mantel-Haenszel test were done to evaluate univariate and bivariate relationships between lipid ratios and premature MI. Logistic regression analysis conducted to evaluate multivariate adjusted relations between first premature MI attack and five categories of TC/HDL-C ratios. Analyses were done by predictive analytics software and solutions (PAS version 22). All statistical comparisons were assumed to be significant at $P<0.05$.

RESULTS

This study enrolled 1222 MI cases of both women and men. Table 1 shows baseline quantitative characteristics among cases and controls.

Table 2 demonstrates categorical CAD risk factors among two study groups.

Table 3 shows the comparison of two study groups across TC/HDL-C ratio categories.

Cases and controls demonstrate a statistically significant differences across five subgroups of the

Table 1: Comparison of quantitative factors among cases and controls

Variables	Cases	Controls	p
	Mean ± SD		
Age	45.84±5.96	67.72±7.72	0.001
Systolic hypertension	12.30±2.31	12.69±2.90	0.007
Diastolic hypertension	7.82±1.47	7.88±1.36	0.92
Fasting blood sugar	136.22±67.62	145.32±73.14	0.025
Cholesterol	210.22±50.76	199.47±58.50	0.001
Triglyceride	184.94±100.20	146.25±79.27	0.001
HDL- Cholesterol	41.35±14.08	42.13±13.28	0.32
LDL- Cholesterol	133.46±43.72	125.90±39.43	0.002
Cholesterol /HDL-C	5.52±1.92	5.06±1.81	0.001
Triglyceride/HDL-C	5.05±3.29	3.84±2.53	0.001
LDL-C/HDL-C	3.53±1.54	3.24±1.35	0.001

SD: Standard deviation; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol

Table 2: Distribution of categorical factors between cases and controls

Variables	Cases	Controls	p
	Number (%)		
Gender			
Female	68 (13.0)	212 (30.4)	0.001
Male	455 (87.0)	485 (69.6)	
Smoking			
Yes	301 (57.6)	233 (33.4)	0.001
No	222 (42.4)	464 (66.6)	
Family history of premature CAD			
Yes	116 (22.3)	78 (11.2)	0.001
No	404 (77.7)	618 (88.8)	
Fasting blood sugar (mg/dl)			
> 126	309 (61.2)	339 (54.8)	0.027
≤ 126	196 (38.8)	313 (45.2)	
Cholesterol (mg/dl)			
> 200 Mg/dl	0 (0.0)	0 (0.0%)	-
≤ 200Mg/dl	522 (100)	699 (100)	
Triglyceride (mg/dl)			
> 200 Mg/dl	0 (0.0)	0 (0.0)	-
≤ 200Mg/dl	523 (100)	699 (100)	
HDL-cholesterol (mg/dl)			
> 45 Mg/dl	363 (69.5)	463 (66.2)	0.22
≤ 45Mg/dl	159 (30.5)	236 (33.8)	
LDL-cholesterol (mg/dl)			
> 130Mg/dl	257 (49.5)	400 (57.2)	0.008
≤ 130Mg/dl	262 (50.5)	299 (42.8)	

CAD: Coronary artery disease; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol

Table 3: Comparison of five categories of total cholesterol/High density lipoprotein cholesterol ratio among cases and controls

Categories	Cases	Controls
	Number (%)	
Very low risk	4 (0.7)	27 (3.8)
Low risk	15 (2.8)	62 (9.0)
Average risk	161 (30.8)	264 (37.8)
Moderate risk	307 (58.7)	314 (44.9)
High risk	36 (7.0)	31 (4.5)
Total	523 (100)	698 (100)

TC/HDL-C ratio (p=0.001).

Mantel-Haenszel relationship between MI under 55 years and different subgroups of the TC/HDL-C ratio revealed a very interesting results. MI under age of 55 years is significantly related to five categories of the TC/HDL-C ratio among nonsmokers (p=0.01), family history of premature CAD (p=0.01), fasting blood sugar>126mg/dl (p=0.005), cholesterol<200mg/dl (p=0.006), triglyceride<200mg/dl (p=0.006), HDL-C≤45mg/dl (p=0.006), and LDL-C<130mg/dl (p=0.008).

Multivariable adjusted relations were evaluated in a logistic regression model. Parameter estimation in regression analysis were made based on adjustment for sex, hypertension, body mass index, family history of premature CAD, smoking habit and LDL-C concentration. After adjustment for potential confounding factor outputs of regression analysis show that TC/HDL-C ratio is significantly related with the occurrence of MI under 55years (p=0.004).

Besides, patients who are in the categories of very low risk (p=0.016) and low risk (p=0.032) compare to patients having high risk categories according to the subgroups of TC/HDL-C ratio show attenuated risk for developing MI.

Patients with very low risk category of TC/HDL-C ratio estimated OR=0.18 with 95% confidence interval (CI) (0.04-0.72) for developing MI under 55 years compared to high risk category of TC/HDL-C ratio.

Moreover, CAD patients having low risk category of TC/HDL-C ratio in comparison with high risk category of the ratio had OR=0.26 95% CI (0.07-0.89).

Therefore, very low risk category of the TC/HDL-C ratio which present the amount of 3.3-3.4 of this ratio accompanied with low risk subgroups which comprises of 3.8-4 of the TC/HDL-C ratio compare to high risk category of the ratio attenuate the risk of developing MI under 55 years p<0.05.

Discussion

The ratio of TC/HDL-C has been recognized as one of the most feasible and strong predictor of developing future cardiovascular events (1, 2, 5, 6). This study provides evidence about the role of lower concentration of TC/HDL-C ratio in attenuation of the risk of MI under55 years. Therefore, aggressive treatment strategies for lowering TC/HDL-C ratio could be immediate clinical implication of our findings.

Our study results can be translated as preventive measures including: mitigation of cholesterol concentration and rising of HDL-C concentration as much as possible in general population and also among victims of coronary events. Because we found that mitigation of the level of TC/HDL-C ratio from low risk to very low risk category will attenuate the risk of MI under55 years about 8%.

In the epidemic situation of CAD in our population we observed that rate of MI attack under 55 years has been raised. Previous evidence of our population reported a high level of TC/HDL-C ratio including 4.70 and 4.72 for individual with age under55 and above 55 years, respectively (4). So we need to plan effective and more practical preventive strategies to dedicate interventions at national level which might be efficacious and inclusive. Such a preventive measure must be based on research findings associated with previous valid and reliable guidelines.

Our multivariable adjusted findings show patients possessing lower level of TC/HDL-C ratio mitigate their risk of developing MI attacks. Results of the previously published evidence demonstrate that trend of increment in TC/HDL-C ratio above age of 60 years contain a significant augmentative pattern and such patients more enjoy attenuation of the TC/HDL-C level (5). Mitigation of the atherogenic ratio of TC/HDL-C has encompassed beneficial effect in both primary, and secondary prevention (10, 14). Measurement and properly interpretation of the TC/HDL-C ratio amounts is demanded in medical practice, especially when abdominal obesity and insulin resistance exist (6).

It has been proven that HDL-C is a cardio protective lipid and its low concentration must be a target for management (7). The importance of the HDL-c role in preventive cardiovascular medicine is even higher in primary prevention setting (2, 11, 15, 16). Recent genetic researches endorsed the role of HDL-C in prediction of future vascular events (17, 18). Individuals with premature CAD events demonstrate lower level of HDL-C (14). In secondary prevention trials augmentation of HDL-C concentration were found to be associated with lower mortality rate (19). Our finding shows that apart from the ratio of TC/HDL-C, CAD risk factors including: high concentration of cholesterol, triglyceride, LDL-C, TG/HDL-C and LDL-C/HDL-C associated with possessing family history of premature CAD, smoking and male gender were more common in patients with premature MI. however fasting blood sugar and systolic blood pressure were found to be lower in this cases. In comparison with a large cohort of healthy individuals we observed a high concentration of cholesterol, triglyceride, LDL-C, and blood sugar accompanied with higher rate of smoking, systolic and diastolic hypertension, and the ratio of TG/HDL-C among healthy people with age above 55 years (4). Beneficial effect of the attenuation of TC/HDL-C ratio in the primary prevention setting especially in age under 50 years considered to be beyond expectations. Unfortunately, primary preventive services for cardiovascular disease are suboptimal (20). We recommend measurement of TC/HDL-C ratio should be a part of every cardiovascular health check in both women and men. Especially in women with normal angiogram who demonstrate the symptom and signs of cardiac ischemia (21). Because in premature CAD dyslipoproteinemia is one of the most important risk factor for developing future cardiovascular events, we should perform more rigorous guidelines including measurement and management of atherogenic lipid concentrations and lipid ratios in our population.

Our study has numerous strengths that make the results of a case control design valid and accurate. We matched the cases and controls on body mass index and diastolic hypertension in the design phase of the study, controlled the role of potential confounders in bivariate analysis and finally adjusted the role of remaining confounders in a multivariable adjusted regression analysis. We recruited incident cases to the study to mitigate the impact of time and duration of the disease on the pre specified relations. CAD risk factor assessments were based on standardized protocol for measurements concurrently in both study populations. MI detection were based on clinical presentation, enzymatic findings, electrocardiographic, echocardiography, and angiographic ally confirmed findings.

Limitation

Limitation of our study should be considered as the limitations of observational case control designs. We will prefer to measure the novel CAD risk factors to develop a more precise risk stratification models.

Conclusions

Our study results can be translated as preventive measures including: mitigation of cholesterol concentration and rising of HDL-C concentration as much as possible in general population and also among victims of coronary events. We found that mitigation of the level of TC/HDL-C ratio from low risk to very low risk category will attenuate the risk of MI under55 years about 8%. Therefore, aggressive treatment strategies for lowering TC/HDL-C ratio could be immediate clinical implication of our findings.

Authors' contribution

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

Conflict of interest

The authors declared that there is no conflict of interest.

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