Association of total cholesterol and HDL-C levels and outcome in coronary heart disease patients with heart failure

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Abstract

The aim of the study was to evaluate associations of total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) levels with prognosis in coronary heart disease (CHD) patients with heart failure (HF).

Patients who were angiographical-diagnosis of CHD and echocardiographical-diagnosis of left ventricular ejection fraction (LVEF) < 45% were enrolled. Baseline characteristics were collected and association of TC and HDL-C levels with rehospitalization for HF and all-cause mortality was assessed.

A total of 118 patients were recruited. Mean age was 58.6 ± 10.9 years and male accounted for 65%. Mean LVEF was 39.5 ± 4.0%. Twenty-eight patients were rehospitalized for HF and 6 patients were dead. In patients with poor prognosis, lower body mass index (BMI), TC, HDL-C and albumin while higher high sensitivity C-reactive protein (Hs-CRP) was observed. TC was positively correlated with BMI and albumin, and HDL-C was inversely correlated with Hs-CRP. The associations of TC level and rehospitalization for HF and all-cause mortality were attenuated but consistently significant through model 1 to 4, with odds ratio (OR) of 0.97 (95% confidence interval [CI]: 0.92–0.99). Associations of HDL-C level and rehospitalization for HF and all-cause mortality were also consistently significant through model 1 to 4, with OR of 0.95 (95% CI: 0.90–0.98). Strength of association was attenuated prominently in model 3 after adjusted for Hs-CRP, and no change was observed after further adjusted for BMI and albumin.

Higher baseline TC and HDL-C levels are associated with better outcome in CHD patients with HF.

Abbreviations: ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, CHD = coronary heart disease, CI = confidence interval, DBP = diastolic blood pressure, HDL-C = high-density lipoprotein cholesterol, HF = heart failure, HR = heart rate, Hs-CRP = high sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro B natriuretic protein, NYHA = New York Heart Association, OR = odds ratio, SBP = systolic blood pressure, TC = total cholesterol.

Keywords: cholesterol, heart failure, prognosis

1. Introduction

Heart failure (HF) is a major cause of morbidity and mortality around the world.[1] Epidemiological studies have shown that 5 years' survival rate of HF patients is only 50%[1] and most HF is attributed to coronary heart disease (CHD),[2] which now affects more than 10 millions people in China.

Dyslipidemia featured by increased serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and decreased high-density lipoprotein cholesterol (HDL-C) is a major risk factor of CHD.[3,4] Theoretically, reducing TC and LDL-C levels would not only decrease the incidence of CHD as

evidenced by previous clinical trials but may also improve HF patients' outcomes. Nevertheless, 2 randomized controlled trials showed no mortality benefit of rosuvastatin therapy in HF patients,[5,6] despite substantial reduction of TC and LDL-C was achieved. In contrast, some observational studies have indicated that higher TC level is associated with better survival outcome in HF patients[7,8] and the underlying mechanisms are elusive which deserve further investigation.

In our present study, we use a retrospective design to evaluate the associations of baseline TC and HDL-C levels with rehospitalization for HF symptoms deterioration and all-cause mortality in CHD patients with reduced ejection fraction, and potential mechanisms related to these associations will also be investigated.

2. Methods

2.1. Studied subjects

We searched patients admitted in our hospital from January to December of 2015 in the medical document system and patients who were qualified to the inclusion criteria in terms of angiographically diagnosed with CHD and echocardiographically diagnosed with left ventricular ejection fraction (LVEF) < 45% were enrolled and those with normal LVEF (≥ 45%) were excluded. Since it was a retrospective study and thus no informed consent could be obtained. Present study was approved by the Clinical Research Ethic Committee of Liuzhou General Hospital.

2.2. Data collection

Baseline data were collected and recorded in case report form by 2 investigators independently and re-checked by another 2 investigators together if there were inconsistent.

2.3. Studied outcomes

Studied outcomes were collected since patients' discharge and studied outcomes were a composite of rehospitalization for HF symptoms deterioration and all-cause mortality.

2.4. Statistical analysis

Continuous variables are presented with mean ± SD and categorical variables are presented with number and frequency. Statistical significance of differences is analyzed using Student t test or Mann–Whitney U test for continuous variables as appropriate and the chi-square or Fisher exact test for categorical variables as appropriate. Pearson correlation analysis or Spearman rank correlation analysis was used to analyze the relationships between TC and HDL-C levels with indexes of interest as appropriate. Logistic regression analysis was applied to analyze odds ratio (OR) and associated 95% confidence intervals (CI) of baseline TC and HDL-C levels with studied outcomes. Statistical analysis is conducted by using SPSS 17.0 (SPSS Inc, Chicago, IL). All of the statistical tests were 2-sided and considered statistically significant if $P < 0.05$.

3. Results

3.1. Baseline characteristics

A total of 118 patients were recruited and baseline characteristics were shown in Table 1. Mean age was 58.6 ± 10.9 years and male accounted for nearly 65%, and 48.3% and 33.1% of studied subjects had a diagnosis of hypertension and diabetes, respectively. Body mass index (BMI) was 21.4 ± 2.3 kg/m². With respect to laboratory examinations, the TC level was 4.23 ± 0.37 mmol/L, LDL-C 2.71 ± 0.52 mmol/L and HDL-C 0.96 ± 0.18 mmol/L, respectively, and albumin (ALB), high sensitive C-reactive protein (Hs-CRP) and N-terminal pro B natriuretic protein (NT-proBNP) levels were 32.7 ± 4.4 g/L, 14.6 ± 6.7 mg/L and 1884 ± 426 pg/mL, respectively. Nearly 70% of studied subjects had multiple-vessels stenoses and mean numbers of stent placement were 2.4 ± 0.8. Mean LVEF was 39.5 ± 4.0%, and 44.1% and 55.9% of studied subjects had cardiac function of New York Heart Association (NYHA)-I/II and NYHA-III/IV, respectively. Notably, all enrolled patients were diagnosed as heart failure based on clinical symptoms such as exertional dyspnea and increased NT-proBNP value. Nearly 72.9%, 67.8%, 88.1%, 82.2%, and 96.6% of studied subjects were prescribed angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), beta-blocker, statins, diuretics, and antiplatelet agents at discharge.

3.2. Studied outcomes and comparisons between groups

Among studied subjects, 28 patients were rehospitalized for HF symptoms deterioration and 6 patients were dead, and these patients were considered together as the poor prognosis group and were compared with subjects with better prognosis. As presented in Table 2, compared to patients with poor prognosis, those with better prognosis were less likely male and were younger ($P < 0.05$ for all comparisons). A trend of lower systolic/

Table 1

Baseline characteristics.

Variables	Studied subjects (n = 118)
Male, n, %	76 (64.4)
Age, y	58.6 ± 10.9
Current smoking, %	60 (50.8)
Alcohol abuse, n, %	19 (16.1)
Family CHD history, n, %	49 (41.5)
Hypertension, n, %	57 (48.3)
Diabetes, n, %	39 (33.1)
SBP, mm Hg	116.2 ± 14.9
DBP, mm Hg	70.9 ± 10.6
HR, bpm	84.6 ± 11.7
Weight, kg	62.6 ± 13.9
BMI, kg/m²	21.4 ± 2.3
TC, mmol/L	4.23 ± 0.37
TG, mmol/L	1.48 ± 0.28
LDL-C, mmol/L	2.71 ± 0.52
HDL-C, mmol/L	0.96 ± 0.18
ALB, g/L	32.7 ± 4.4
Cr, μmol/L	117.6 ± 16.9
BUN, mmol/L	7.1 ± 3.5
ALT, U/L	67.6 ± 11.8
FPG, mmol/L	5.7 ± 0.7
HbA1c, %	6.1 ± 0.8
Hs-CRP, mg/L	14.6 ± 6.7
NT-proBNP, pg/mL	1884 ± 426
One-vessel stenosis, n, %	36 (30.5)
Multiple-vessels stenoses, n, %	82 (69.5)
Number of stent placement	2.4 ± 0.8
ACEI/ARB, n, %	86 (72.9)
Beta-blocker, n, %	80 (67.8)
Statins, n, %	104 (88.1)
Diuretics, n, %	97 (82.2)
Antiplatelet agents, n, %	114 (96.6)
Antidiabetes, n, %	37 (31.4)
LVEF, %	39.5 ± 4.0
NYHA-I/II, n, %	52 (44.1)
NYHA-III/IV, n, %	66 (55.9)

ACEI/ARB = angiotensin converting-enzyme inhibitor/angiotensin receptor blocker, ALB = albumin, ALT = alanine aminotransferase, BMI = body mass index (weight in kilogram divided by height in square of meter), bpm = beat per minute, BUN = blood urine nitrogen, CHD = coronary heart disease, Cr = creatinine, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, HR = heart rate, Hs-CRP = high sensitive C-reactive protein, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, NT-proBNP = N terminal-pro B natriuretic protein, NYHA = New York Heart Association, SBP/DBP = systolic/diastolic blood pressure, TC = total cholesterol, TG = triglyceride.

diastolic blood pressure (SBP/DBP) and higher heart rate (HR) were observed in patients with poor prognosis. Lower weight, BMI, TC, HDL-C and ALB levels, whereas higher Hs-CRP and NT-proBNP levels were also observed in patients with poor prognosis ($P < 0.05$ for all comparisons). No significant differences in medications prescription at discharge except for beta-blocker were observed. Patients with poor prognosis had lower LVEF (36.1 ± 4.2% versus 40.8 ± 3.7%, $P < 0.05$) and had more severe HF as indexed by the NYHA classification (NYHA-III/IV: 61.8% vs 53.6%, $P < 0.05$).

3.3. Relationship between TC and HDL-C with indexes of interest

As presented in Table 3, the TC level was positively correlated with weight, BMI and ALB level while inversely correlated with the NYHA classification. The HDL-C level was inversely correlated with Hs-CRP level and the NYHA classification.

Table 2

Comparisons between poor and better prognosis groups.

Variables	Poor prognosis (n = 34)	Better prognosis (n = 84)
Male, n, %	26 (76.5)*	50 (59.5)
Age, y	61.3 ± 8.6*	57.1 ± 11.2
Current smoking, %	17 (50.0)	43 (51.2)
Alcohol abuse, n, %	6 (17.6)	13 (15.5)
Family CHD history, n, %	14 (41.2)	49 (41.7)
Hypertension, n, %	16 (47.1)	41 (48.8)
Diabetes, n, %	11 (32.4)	39 (33.3)
SBP, mm Hg	110.6 ± 12.5	119.7 ± 10.5
DBP, mm Hg	68.8 ± 7.4	72.6 ± 11.2
HR, bpm	89.4 ± 10.6	82.2 ± 13.3
Weight, kg	61.8 ± 11.6*	64.4 ± 12.4
BMI, kg/m^2	19.6 ± 2.2*	22.8 ± 2.0
TC, mmol/L	3.97 ± 0.31*	4.40 ± 0.33
TG, mmol/L	1.47 ± 0.20	1.49 ± 0.22
LDL-C, mmol/L	2.58 ± 0.45	2.93 ± 0.55
HDL-C, mmol/L	0.88 ± 0.17*	1.09 ± 0.22
ALB, g/L	30.8 ± 5.6*	35.4 ± 4.7
Cr, μmol/L	111.4 ± 14.6	118.2 ± 13.7
BUN, mmol/L	7.0 ± 3.3	7.3 ± 3.4
ALT, U/L	68.2 ± 13.1	66.7 ± 10.5
FPG, mmol/L	5.5 ± 0.7	5.8 ± 0.6
HbA1c, %	6.0 ± 0.7	6.2 ± 0.5
Hs-CRP, mg/L	16.2 ± 6.0*	11.3 ± 7.2
NT-proBNP, pg/mL	1936 ± 401*	1801 ± 455
One-vessel stenosis, n, %	10 (29.4)	26 (31.0)
Multiple-vessels stenoses, n, %	24 (70.6)	58 (69.0)
Number of stent placement	2.3 ± 0.5	2.5 ± 0.7
ACEI/ARB, n, %	25 (73.5)	61 (72.6)
Beta-blocker, n, %	22 (64.7)*	58 (69.0)
Statins, n, %	30 (88.2)	74 (88.1)
Diuretics, n, %	28 (82.4)	69 (82.1)
Anti-platelet agents, n, %	32 (94.1)	82 (97.6)
Anti-diabetes, n, %	11 (32.4)	26 (31.0)
LVEF, %	36.1 ± 4.2*	40.8 ± 3.7
NYHA-I/II, n, %	12 (35.3)*	40 (47.6)
NYHA-III/IV, n, %	21 (61.8)*	45 (53.6)

ACEI/ARB = angiotensin converting-enzyme inhibitor/angiotensin receptor blocker, ALB = albumin, ALT = alanine aminotransferase, BMI = body mass index (weight in kilogram divided by height in square of meter), bpm = beat per minute, BUN = blood urine nitrogen, CHD = coronary heart disease, Cr = creatinine, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, HR = heart rate, Hs-CRP = high sensitive C-reactive protein, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, NT-proBNP = N terminal-pro B natriuretic protein, NYHA = New York Heart Association, SBP/DBP = systolic/diastolic blood pressure, TC = total cholesterol, TG = triglyceride.

* $P < 0.05$ versus better prognosis group.

3.4. Logistic regression analysis

Logistic regression analysis was performed to evaluate the associations of TC and HDL-C levels with studied outcomes, respectively. As presented in Table 4, the associations between TC level with rehospitalization and all-cause mortality were attenuated but consistently significant through model 1 to model 4, with OR of 0.97 (95% CI: 0.92–0.99) after ultimately adjusted for BMI and ALB in model 4. The associations between HDL-C level with rehospitalization and all-cause mortality were also consistently significant through model 1 to model 4, with OR of 0.95 (95% CI: 0.90–0.98). Notably, strength of association was attenuated prominently in model 3 after adjusted for Hs-CRP, and no change was observed after further adjusted for BMI and ALB in model 4.

Table 3

Relationship between TC and HDL-C with indexes of interest.

Variables	Correlation coefficient	
	TC	HDL-C
Weight	0.304*	0.096
BMI	0.369*	0.104
ALB	0.416*	0.113
Hs-CRP	−0.084	−0.267*
LVEF	0.026	0.033
NYHA classification	−0.248*	−0.223*

ALB = albumin, BMI = body mass index (weight in kilogram divided by height in square of meter), HDL-C = high-density lipoprotein cholesterol, Hs-CRP = high sensitive C-reactive protein, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, TC = total cholesterol.

* $P < 0.05$; relationship between TC and HDL-C with weight, BMI, ALB, Hs-CRP and LVEF were analyzed by Pearson correlation analysis, and with NYHA classification was analyzed by Spearman rank correlation analysis

4. Discussion

In general, our present study has 2 major findings. First, we observe that in CHD patients with LVEF < 45%, higher baseline TC and HDL-C levels are associated with lower risk of rehospitalization for HF symptoms deterioration and all-cause mortality. Second, underlying mechanisms associated with these favorable effects of higher baseline TC and HDL-C levels may be different. Future randomized controlled trials are necessary to evaluate whether increasing TC and HDL-C levels will confer cardiovascular benefits in CHD patients with reduced LVEF.

Despite great advancements in CHD prevention and treatment have been achieved in recent decades, the prognosis of CHD patients with HF remain poor with 5 years' mortality rate up to 50%. A substantial number of factors associated with poor prognosis of HF have been identified in epidemiological studies and among them malnutrition appears to play a major role.[9,10] Owing to intestinal edema, tachycardia, and dyspnea, most HF patients are in a metabolically demanding condition which leads them to a malnutritional status. Indeed, it has been reported that HF patients commonly have lower ALB and cholesterol levels. Consistent to previous findings, results from our present study also showed that CHD patients with reduced LVEF had relatively lower serum TC, LDL-C, and HDL-C levels. Although it might be possible that statins therapy would reduce serum cholesterol level, nevertheless, the serum ALB level (32.7 ± 4.4 g/L) below the normal range (≥ 40 g/L) might also directly indicate that patients in present study were in a malnutritional condition.

Table 4

Logistic regression analysis.

	TC (OR and 95% CI)	HDL-C (OR and 95% CI)
Model 1	0.81 (0.76–0.89)	0.76 (0.70–0.82)
Model 2	0.83 (0.81–0.92)	0.82 (0.74–0.87)
Model 3	0.85 (0.84–0.90)	0.94 (0.88–0.98)
Model 4	0.97 (0.92–0.99)	0.95 (0.90–0.98)

CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, OR = odds ratio, TC = total cholesterol.

Denote: Model 1 adjusted for age, gender, and smoking; Model 2 adjusted for age, gender, smoking, hypertension, diabetes, multiple-vessels stenoses and number of stent placement, ACEI/ARB, beta-blocker, statins, LVEF and NYHA classification; Model 3 adjusted for age, gender, smoking, hypertension, diabetes, multiple-vessels stenoses and number of stent placement, ACEI/ARB, beta-blocker, statins, LVEF and NYHA classification, and Hs-CRP; Model 4 adjusted for age, gender, smoking, hypertension, diabetes, multiple-vessels stenoses and number of stent placement, ACEI/ARB, beta-blocker, statins, LVEF and NYHA classification, Hs-CRP, BMI and ALB.

Total cholesterol indeed is a sensitive nutritional marker rather than a villain of atherosclerotic cardiovascular diseases. Reverse epidemiology regarding high cholesterol level, BMI and blood pressure are associated with better survival outcome in HF patients were reported by previous epidemiological studies.[3,11,12] The mechanisms underlying these findings are attributed to the protective effects of cholesterol on HF patients. For example, cholesterol on the 1 hand is a major energy resource, and in HF patients, energy-deprivation superimposes hypo-perfusion would promote renal and liver dysfunction which in turn cause HF symptom deterioration.[13] Indeed, data from our present study supported this notion. Compared to patients with better prognosis, those with poor prognosis not only had significantly lower levels of TC and ALB, but also had lower weight, BMI and SBP/DBP. These indexes together indicated that HF patients with a debilitated condition were associated with a poor prognosis. On the other hand, reduced circulating cholesterol-rich lipoprotein level would lead to circulating endotoxin elevation which stimulates excessive inflammation.[10,14] Significantly higher serum Hs-CRP level in patients with poor prognosis also supported this concept.[15] Interestingly, the Pearson correlation analysis had not showed significant correlation between serum TC level with Hs-CRP level, and multivariate regression analysis also showed no significant impact of Hs-CRP adjustment for the association between TC level and studied outcome in model 3. Nevertheless, in model 4, after adjusted for BMI and ALB level, the association was attenuated although remain significant. Taken together, it was conceivable that outcome benefits associated with higher baseline TC level might be attributed to its function of nutrition and energy resource.

Fewer studies have evaluated the association of HDL-C and outcome in CHD patients with HF. HDL-C has been deemed as good cholesterol owing to its anti-inflammation, anti-oxidation and cholesterol-reverse transport virtues.[16–18] Nevertheless, whether these benefits could translate to clinical benefit is unknown. Compared to patients with poor prognosis, those with better prognosis had higher HDL-C level, and HDL-C level was inversely correlated with Hs-CRP level and the NYHA classification. Furthermore, in the multivariate regression analysis, after adjusted for Hs-CRP, association of HDL-C and outcome was prominently attenuated although remained significant. These data together suggested that different from TC, outcome benefits associated with high HDL-C level might be attributed to its function of anti-inflammation.[18]

There were limitations of our present study. First, a retrospective design could not allow us to draw causal relationship between TC and HDL-C with studied outcomes in CHD patients with HF. Second, relatively small sample size may not be powerful to identify other potential important differences between patients with better and poor prognosis. Third, owing to small sample size, potential biases could not be identified despite we extensively adjusted for confounding factors.

5. Conclusion

Data from our present study indicate that in CHD patients with LVEF < 45%, higher baseline TC and HDL-C levels are associated with fewer rehospitalization for HF symptom deterioration and all-cause mortality, and the mechanisms associated with these benefits of TC and HDL-C are different. Future clinical trials are necessary to address whether increasing TC and HDL-C levels could improve HF patients' outcomes.

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