The triglyceride paradox in the mortality of coronary artery disease

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Abstract

Background: The role of triglyceride (TG) in secondary prevention of patients with coronary artery disease (CAD) was debated. In the present study, we assessed the association between admission TG levels and long-term mortality risk in CAD patients.

Methods: A retrospective analysis was conducted from a single registered database. 3061 consecutive patients with CAD confirmed by coronary angiography were enrolled and were grouped into 3 categories by the tertiles of admission serum TG levels. The primary end point in this study was all-cause mortality and the secondary end point was cardiovascular mortality.

Results: The mean follow-up time was 26.9 ± 13.6 months and death events occurred in 258 cases and cardiovascular death events occurred in 146 cases. Cumulative survival curves indicated that the risk of all-cause death decreased with increasing TG level (Tertile 1 vs. Tertile 2 vs. Tertile 3 = 10.3% vs. 8.6% vs. 6.3%, log rank test for overall p = 0.001). Cox regression analysis showed an independent correlation between TG level and risk of all-cause mortality (hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.58–0.86) and cardiovascular mortality (HR 0.67, 95% CI 0.51–0.89) in total patients with CAD. Subgroup analysis found the similar results in patients with acute coronary syndrome and acute myocardial infarction.

Conclusions: This study found an inverse association between TG levels and mortality risk in CAD patients, which suggests that the “TG paradox” may exist in CAD patients.

Trial registration: ChiCTR, ChiCTR-OOC-17010433. Registered 17 February 2017 - Retrospectively registered.

Keywords: Prognosis, Hypertriglyceridemia, Paradox

Introduction

Hypertriglyceridemia (HTG) is considered a risk factor for atherosclerotic cardiovascular disease (ASCVD) [1]. Epidemiological studies showed that coronary artery disease (CAD) patients have higher triglyceride (TG) levels than the general population [2, 3]. Additionally, cohort studies showed that HTG can increase the risk of suffering from CAD [4–6]. However, the association between TG and ASCVD risk has been controversial. A series of studies suggested that there is no independent association between HTG and ASCVD risk after multifactor adjustment for cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) [7]. The role of HTG was also debated in secondary prevention studies of patients who suffer from CAD. Some studies suggested that HTG increases the mortality risk in patients with CAD [8, 9]; however, other studies suggested that there is no association between the two factors [10]. Several recent studies found an inverse association between admission TG level and mortality risk in stroke patients; these studies then proposed the concept of the “TG paradox” [11–14]. As one of ASCVD, CAD has the similar pathophysiological mechanism. Whether a similar TG paradox exists in CAD patients remains unclear.

In the present study, we assessed the association between admission TG levels and long-term mortality risk...
in CAD patients through analyzing a single-center cohort of 3061 consecutively enrolled patients with CAD.

Methods

Study population

The data source for this investigation was the West China Hospital CAD database. This single center database prospectively includes all the CAD or high risk patients undergoing angiography in West China Hospital affiliated to Sichuan University. For this analysis, we enrolled consecutive patients with CAD from January 2009 to September 2012 of the database. Patients with CAD were eligible for inclusion if they were restricted to participants with angiographic evidence of ≥50% stenosis in ≥1 coronary vessels. The criteria of acute myocardial infarction (AMI) was diagnosed on the basis of the triad of chest pain, electrocardiogram changes, and elevated serum cardiac enzyme levels [15]. The criteria of stable angina pectoris was diagnosed on the basis of the symptom of exertional chest pain, angiographic evidence, and/or electrocardiogram changes, and normal serum cardiac enzyme levels. The criteria of unstable angina pectoris was diagnosed on the basis of criteria of AP and ischemic chest discomfort that increased or occurred at rest. The acute coronary syndrome (ACS) included AMI and unstable angina pectoris. The exclusion criteria included malignancies, pregnancy, end stage renal disease and severe liver or hematological diseases. These inclusion and exclusion criteria were met by 3365 continuously enrolled CAD patients. After excluding patients with loss of follow-up (n = 287) and missing data of TG (n = 17), 3061 patients were included in the data analysis. The study protocol was approved by ethics committee of West China Hospital, Sichuan University in accordance with the Declaration of Helsinki. All subjects provided written informed consent before enrolment.

Baseline characteristics

Demographic data, medical history, cardiovascular risk factor, vital signs at admission, medication at discharge, and final diagnosis were obtained from the patients’ electronic medical records and reviewed by a trained study coordinator. Blood sample were collected at admission, and serum lipid including TG, liver and kidney function, blood glucose, etc. were analyzed in the department of Laboratory Medicine, West China hospital, accredited by the College of American Pathologists. TG level was measured by enzymatic colorimetric assay (Cobas 8000 C702 Chemistry autoanalyzer, Roche Diagnostics, Germany). Hypertension was defined as those with systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and/or those receiving antihypertensive medications. Diabetes mellitus (DM) was diagnosed in patients who had previously undergone dietary treatment for diabetes, had received additional oral antidiabetic or insulin medication or had a current fasting blood glucose level of ≥7.0 mmol/L or random blood glucose level ≥ 11.1 mmol/L. Patients received care according to the usual practice; treatment was not affected by participation in this study.

Follow-up and end points

The follow-up period ended on January 2013. Follow-up information was collected through contact with patients’ physicians, patients or their family. All data were corroborated with the hospital records. The primary end point in this study was all-cause mortality and the secondary end point was cardiovascular death, as documented in the database. Death was considered cardiac when it was caused by acute MI, significant arrhythmias, or refractory heart failure. Sudden unexpected death occurring without another explanation was included as cardiovascular death.

Statistical analyses

We conducted the post-hoc analysis on a retrospective basis. Baseline demographics and clinical characteristics were compared among patients categorized by the tertiles of admission TG level in three groups. Continuous variables are expressed as the mean ± standard deviation (SD), and categorical variables are reported as counts and percentages. Analysis of variance (ANOVA) and chi-squared tests were used to test for differences among groups for continuous and categorical variables, respectively. To determine the association between TG levels and all-cause mortality, Kaplan–Meier curves by tertiles of TG level were constructed and examined using the log-rank test for comparison. Cox proportional hazards models were used to evaluate the relationship of tertiles of TG level with all-cause and cardiovascular mortality, initially unadjusted and subsequently adjusting for several covariates: age, sex, medical history [pre-hypertension, pre-diabetes mellitus, pre-myocardial infarction, pre- percutaneous coronary intervention (pre-PCI), pre-cardiac artery bypass graft (pre-CABG)], admission examination [systolic blood pressure, heart rate, body mass index (BMI) and Global Registry of Acute Coronary Events (GRACE) score], admission lab test (blood glucose, serum creatinine, LDL-C and HDL-C), and severity of CAD (left main artery, three vessel diseases and number of stents) [16–18]. Cox proportional hazards regression models were also used to investigate the independent effect of TG level on all-cause and cardiovascular mortality in overall CAD patients and subgroups. Two-sided p values of less than 0.05 indicated statistical significance. All analyses were performed with Stata MP (version 14.0).
Results
A total of 3061 patients with CAD were included in the study. The average age was 64.4 ± 10.7 years, and men accounted for 79.4% of the patients. Serum TG levels were measured within 24 h after admission. The patients were divided into three groups according to the tertiles.

| Table 1 Baseline characteristics of the study population |
|---------------------------------------------------------|
| Characteristics                                      | Total  | Tertile 1 | Tertile 2 | Tertile 3 | p value |
|---------------------------------------------------------|
| No. of patients                                        | n = 3061 | n = 1039 | n = 1019 | n = 1003 |         |
| Age, yrs                                               | 64.41 (10.68) | 66.36 (10.21) | 64.55 (10.33) | 62.24 (11.09) | < 0.001 |
| Gender, men, n (%)                                     | 2429 (79.4) | 861 (28.9) | 790 (77.5) | 778 (77.6) | 0.003   |
| Medical history                                        |         |         |         |         |         |
| Pre-hypertension, n (%)                                | 1684 (55.3) | 568 (54.9) | 581 (57.2) | 535 (53.7) | 0.270   |
| Pre-diabetes mellitus, n (%)                           | 665 (21.8) | 187 (18.1) | 259 (25.5) | 219 (22.0) | < 0.001 |
| Pre-myocardial infarction, n (%)                       | 830 (27.1) | 303 (29.2) | 283 (27.8) | 244 (24.3) | 0.041   |
| Pre-PCI, n(%)                                          | 365 (11.9) | 143 (13.8) | 114 (11.2) | 108 (10.8) | 0.076   |
| Pre-CABG, n(%)                                         | 34 (1.1) | 9 (0.9) | 13 (1.3) | 12 (1.2) | 0.642   |
| At admission                                           |         |         |         |         |         |
| Systolic blood pressure, mm Hg                         | 130.72 (22.33) | 129.09 (23.12) | 131.21 (22.92) | 131.91 (20.76) | 0.013   |
| Diastolic blood pressure, mm Hg                        | 76.49 (12.57) | 75.31 (12.76) | 76.58 (12.38) | 77.62 (12.46) | < 0.001 |
| Heart rate, beats/min                                  | 74.34 (22.98) | 74.88 (29.59) | 74.30 (22.92) | 73.82 (13.11) | 0.584   |
| Killip classification ≥ II, n (%)                      | 345 (11.3) | 136 (13.1) | 121 (11.9) | 88 (8.8) | 0.007   |
| GRACE score                                            | 92.74 (26.00) | 96.44 (25.92) | 93.32 (25.94) | 88.30 (25.49) | < 0.001 |
| BMI                                                    | 24.40 (6.75) | 23.55 (3.34) | 24.72 (10.34) | 24.94 (4.23) | < 0.001 |
| Laboratory values                                      |         |         |         |         |         |
| Serum creatinine, μmol/L                               | 93.90 (50.39) | 89.46 (30.49) | 96.19 (57.84) | 96.19 (58.01) | 0.002   |
| Blood glucose, mmol/L                                  | 6.95 (3.13) | 6.57 (2.75) | 7.09 (3.27) | 7.20 (3.294) | < 0.001 |
| Total cholesterol, mmol/L                              | 4.07 (1.12) | 3.69 (0.94) | 4.02 (1.00) | 4.52 (1.25) | < 0.001 |
| TG, mmol/L                                             | 1.75 (1.13) | 0.91 (0.18) | 1.48 (0.19) | 2.89 (1.32) | < 0.001 |
| LDL, mmol/L                                            | 2.46 (3.48) | 2.14 (0.80) | 2.41 (0.89) | 2.83 (5.95) | < 0.001 |
| HDL, mmol/L                                            | 1.15 (0.35) | 1.26 (0.34) | 1.15 (0.36) | 1.03 (0.31) | < 0.001 |
| Hemoglobin, g/L                                        | 134.39 (31.12) | 131.54 (16.76) | 133.48 (18.05) | 138.28 (48.10) | < 0.001 |
| White blood cell, n×10⁹/L                              | 7.48 (4.94) | 7.13 (3.00) | 7.69 (7.06) | 7.64 (3.78) | 0.017   |
| Severity of CAD                                        |         |         |         |         |         |
| Left main artery, n (%)                                | 284 (9.3) | 95 (9.1) | 102 (10.0) | 87 (8.7) | 0.575   |
| Three vessel diseases, n (%)                           | 795 (26.0) | 246 (23.7) | 280 (27.5) | 269 (26.8) | 0.109   |
| No. of stents                                          | 1.22 (1.22) | 1.17 (1.19) | 1.26 (1.21) | 1.24 (1.27) | 0.195   |
| Diagnose                                               |         |         |         |         |         |
| ACS, n(%)                                              | 2174 (71.0) | 715 (68.8) | 715 (70.2) | 744 (74.2) | 0.022   |
| AMI, n(%)                                              | 636 (20.8) | 219 (21.1) | 213 (20.9) | 204 (20.3) | 0.912   |
| Discharge medications                                  |         |         |         |         |         |
| Aspirin, n (%)                                         | 2812 (91.9) | 951 (91.5) | 938 (92.1) | 923 (92.0) | 0.963   |
| Clopidogrel, n (%)                                     | 2735 (89.3) | 905 (87.1) | 917 (90.0) | 913 (91.0) | 0.088   |
| Statins, n (%)                                         | 2754 (90.0) | 934 (89.9) | 921 (90.4) | 899 (89.6) | 0.958   |
| ACE inhibitors or ARBs, n (%)                          | 1753 (57.3) | 601 (57.8) | 572 (56.1) | 580 (57.8) | 0.950   |
| Beta-receptor blockers, n (%)                          | 2028 (66.3) | 634 (61.0) | 671 (65.8) | 723 (72.1) | < 0.001 |

Data are expressed as means ± SD or counts and percentages, as appropriate.

Abbreviations: BMI body mass index, PCI percutaneous coronary intervention, CABG coronary artery bypass graft, TG triglyceride, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, CAD coronary artery disease, ACE angiotensin-converting enzyme, ARBs angiotensin-receptor blockers, GRACE score Global Registry of Acute Coronary Events score.
of TG levels. As shown by the baseline data distribution in Table 1, the clinical features showed differences among groups. Compared with lower TG level group, higher TG level group corresponded to higher TC and LDL-C levels, but lower HDL level, younger patient age, and better GRACE score.

The 3061 patients were followed up for an average duration of 26.9 ± 13.6 months. Total of death events occurred in 258 cases (mortality rate: 8.4%) during the follow-up period, including 146 cases (cardiovascular mortality rate: 4.8%) of cardiac death. As shown by the cumulative survival curves of groups by tertiles of TG level, the risk of all-cause mortality exhibited an overall rising trend as TG levels decreased (mortality rate, Tertile 1 vs. Tertile 2 vs. Tertile 3, 10.3% vs. 8.6% vs. 6.3%, log rank test for overall $p = 0.001$) (Fig. 1, panel a). The risk analysis of cardiac mortality obtained results similar trend to those mentioned above (cardiovascular mortality rate, Tertile 1 vs. Tertile 2 vs. Tertile 3, 5.9% vs. 4.4% vs. 4.0%, log rank test for overall $p = 0.067$) (Fig. 1, panel b). Even after multifactorial regression, TG level were still inversely correlated with risk of all-cause mortality and cardiovascular mortality (Table 2). Furthermore, similar trends were detected in patients with ACS (Fig. 1, panel c and panel d; and Table 2).

Cox regression analysis showed an independent correlation between TG level and risk of all-cause mortality and cardiovascular mortality in total patients with CAD. Subgroup analysis found the similar results in patients with ACS and AMI, except the cardiac mortality in patients with stable angina pectoris (Table 3).

**Discussions**

This study found an inverse association between TG levels and mortality risk in patients with CAD, which suggests that the “TG paradox” may exist in CAD patients.

The association between TG and ASCVD risk has not been less certain than that for LDL-C for a long time. Some studies suggested that TG has no association with

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**Fig. 1** Kaplan–Meier survival curves for all-cause mortality and cardiovascular mortality patients with coronary artery disease according to triglyceride levels. Panel a and Panel b in total 3061 patients with CAD; Panel c and Panel d in 2174 patients with ACS.
Table 2 Relationship of tertiles of triglyceride level to all-cause mortality in coronary artery disease

| Tertile | All-cause mortality, HR (95% CI) | Cardiovascular mortality, HR (95% CI) |
|---------|----------------------------------|--------------------------------------|
| Tertile 1 | 1.00 (0.59–1.09) | 0.63 (0.33–0.85) |
| Tertile 2 | 0.80 (0.51–0.89) | 0.69 (0.46–0.62) |
| Tertile 3 | 0.69 (0.37–0.95) | 0.69 (0.46–0.81) |

Abbreviations: HR hazard ratio, ACS acute coronary syndrome, CI confidence interval, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, CAD coronary artery disease, BMI body mass index, GRACE score Global Registry of Acute Coronary Events score.

Table 3 Relationship of triglyceride level with all-cause mortality in coronary artery disease and subgroups

| Subgroup                | All-Cause Mortality | Cardiovascular Mortality |
|-------------------------|---------------------|--------------------------|
|                         | HR (95% CI)         | p                        |
| Total patients          | 0.74 (0.62–0.87)    | 0.001                     |
| Unadjusted              | 0.77 (0.60–0.97)    | 0.028                     |
| Adjusted*               | 0.63 (0.58–0.68)    | 0.006                     |
| ACS                     | 0.71 (0.58–0.86)    | 0.017                     |
| Unadjusted              | 0.80 (0.61–1.04)    | 0.096                     |
| Adjusted*               | 0.69 (0.51–0.94)    | 0.018                     |
| AMI                     | 0.63 (0.46–0.87)    | 0.005                     |
| Unadjusted              | 0.53 (0.33–0.85)    | 0.008                     |
| Adjusted*               | 0.50 (0.30–0.86)    | 0.012                     |
| Stable angina pectoris  | 0.74 (0.52–1.06)    | 0.099                     |
| Unadjusted              | 0.62 (0.36–1.06)    | 0.086                     |
| Adjusted*               | 0.59 (0.24–1.16)    | 0.127                     |

Abbreviations: HR hazard ratio, CI confidence interval, ACS acute coronary syndrome, AMI acute myocardial infarction, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, CAD coronary artery disease, BMI body mass index, GRACE score Global Registry of Acute Coronary Events score.

*Triglyceride levels was grouped by the tertiles; †Risk factors adjustment included age, sex, medical history (pre-hypertension, pre-diabetes mellitus, pre-myocardial infarction, pre-PCI and pre-CABG), admission examination (systolic blood pressure, heart rate, BMI and GRACE score), admission lab test (blood glucose, serum creatinine, LDL-C and HDL-C), and severity of CAD (left main artery, three vessel diseases and number of stents).
previously reported that TG levels significantly decrease in ACS patients compared with stable angina pectoris patients within 24 h of onset and the low TG level were associated with the recurrent ischemia and the higher 30-days mortality in ACS patients [35–37]. Third, other basic research reported that HTG may have a potential protective role in vascular lesions. HTG can provide protective effects against fatty acid-induced lip toxicity [38]; additionally, blood lipid levels that are too low are detrimental to maintaining a stable state of cell membranes [39]. Finally, our study included a limited number of adjustment factors for the regression equation, and some unknown risk factors associated with TG might be overlooked, thus exaggerating the role of TG in the secondary prevention of CAD. Therefore, due to lack of large sample prospective study that is specifically designed to address the mechanism underlying this issue, but it is still inconclusive whether TG directly affects the prognosis of CAD patients or just plays a role as an indirect factor. These issues need to be further investigated.

This study has a few limitations. First, the study was a single-center observational study. Despite the multi-factor adjustment, it was difficult to completely avoid selection bias and the remaining confounding factors. Second, observational studies do not positively interfere with any diagnosis and treatment of patients; thus, a random TG measurement, other than the fasting TG, is used for emergency patients. In this study, the fasting TG level was collected from most elective coronary angiography patients (mainly with stable angina pectoris or unstable angina pectoris), while a random TG level was used for most emergency PCI patients (mainly with AMI). Therefore, the TG levels would be more susceptible to the effects of meal and thus increase in high-risk patients. However, in the current study, the percentages of AMI patients were similar in the various TG groups, suggesting that our results were not significantly affected by meals. The last, our analysis included only the measurement of laboratory and heart echocardiography completed within one week after admission of the patients to the hospital, which were not conducted during stable phase.

Conclusion
This study found an inverse association between TG levels and mortality risk in CAD patients, which suggests that the “TG paradox” may exist in CAD patients.

Abbreviations
ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; ANOVA: Analysis of variance; ASCVD: Atherosclerotic cardiovascular disease; BMI: Body mass index; CAD: Coronary artery disease; DBP: Diastolic blood pressure; DM: Diabetes mellitus; ESRD: End stage renal disease; HDL-C: High-density lipoprotein cholesterol; HTG: Hypertriglyceridemia; LDL-C: Low-density lipoprotein cholesterol; MACE: Major adverse cardiac events; NSTEMI: Non-ST elevation myocardial infarction; SBP: Systolic blood pressure; SD: Standard deviation; STEMI: ST elevation myocardial infarction; TC: Cholesterol; TG: Triglyceride

Acknowledgements
Not applicable.

Funding
This study was funded by the National Natural Science Foundation of China (grant number: 81400267 and 81307029, Beijing, China) and the National High-tech Research and Development Program of China [2012AA02A510, Beijing, China].

Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors’ contributions
TLX, MC, DJH and YP participated in study conception and design. FYH, HC, and BTH performed the acquisition of data. TLX, YML, LYB, YWXO and QL participated in analysis and interpretation of data. ZGZ, ZLZ and YP drafted the manuscript and YP, MC, and DJH helped in critical review of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study was conducted after the acquisition of written informed consent from the participating patients and upon the approval by the ethics committee of West China Hospital, Sichuan University.

Consent for publication
If the manuscript is accepted, we approve it for publication in Lipids in Health and Disease.

Competing interests
The authors declare that they have no competing interests.

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Received: 30 October 2018 Accepted: 8 January 2019
Published online: 22 January 2019

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