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Low admission triglyceride and mortality in acute coronary syndrome patients

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Abstract

Background: *The relationship between admission triglyceride (TG) levels and long-term outcomes has not been established in patients with acute coronary syndrome. We tested the hypothesis that patients who develop non-ST segment elevation myocardial infarction (NSTEMI) despite low TG have a worse cardiovascular outcome in the long term.*

Methods: *Patients admitted with NSTEMI between 1 January 1997 and 31 December 2000 and with fasting lipid profiles measured within 24 hours of admission were included for analysis. Baseline characteristics and three-year all-cause mortality were compared between the patients with TG above and below the median. Multivariate analysis was used to determine the predictors of all-cause mortality and adjusted survival was analyzed using the Cox proportional hazard model.*

Results: *Of 517 patients, 395 had TG ≤ 200 mg/dL and 124 had TG > 200 mg/dL. Patients with low TG were more often Caucasian, with no significant differences in gender or severity of coronary artery disease between the two groups. There was a trend for increased all-cause mortality at six months (9% vs 3%, p = 0.045) and three years (13.4% vs 5.6%, p = 0.016) in patients with low TG. In multivariate analysis, low TG level at admission was an independent predictor of increased mortality at three years (adjusted OR 2.5, 95% CI = 1.04–5.9, p = 0.04).*

Conclusions: *In our cohort, lower TG at admission is associated with increased three-year mortality in patients with NSTEMI. Whether this is a result of current therapy, or a marker for worse baseline characteristics, needs to be studied further.* (Cardiol J 2011; 18, 3: 297–303)

Key words: triglyceride, non-ST segment elevation myocardial infarction, mortality

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Introduction

Hyperlipidemia, including hypertriglyceridemia, has been shown to be an independent risk factor for the development of coronary artery disease (CAD) [1–5]. Randomized controlled trials have demonstrated that lipid-lowering therapy improves all-cause mortality and morbidity in patients with risk factors for, and with established, CAD [6–8]. However, many patients still develop atherosclerotic complications despite being on lipid-lowering therapy and/or having target low lipid profiles. In randomized trials involving patients with CAD, major adverse cardiac events (MACE) were noted in 8–22% of patients on lipid-lowering therapy despite achieving target lipid levels [6–14].

Low cholesterol and triglyceride (TG) levels have been associated with poor prognosis in some cardiac and non-cardiac disease states, elderly patients, cancer patients and HIV patients with low cholesterol [15–17]. Several studies have also shown better outcomes for both ischemic and non-ischemic chronic established heart failure patients with higher cholesterol levels including serum TG, than for patients with lower levels [18]. Among stroke patients, low serum TG concentrations, and not low cholesterol, independently predict poor outcome with increased mortality [19]. We have reported before that patients with acute coronary syndrome despite low density lipoprotein cholesterol (LDL) have increased three year mortality [20]. The prognostic value of admission serum TG has not been established in patients with acute coronary syndrome. We wanted to test the hypothesis that patients who have low TG levels at the time of their non-ST segment elevation myocardial infarction (NSTEMI) have worse long term outcomes.

Methods

This study was approved and monitored by the Investigational Review Board of the study hospital. The study population consisted of consecutive patients admitted to the Coronary Intensive Care Unit (CICU) of a tertiary care hospital between January 1997 and December 2000 with admission diagnosis of NSTEMI, who had had their lipid profile measured within 24 hours of hospital admission. Patients whose lipid profiles were measured beyond 24 hours of hospital admission were excluded because the validity of the plasma lipid levels measured beyond 24 hours from the onset of myocardial infarction has been questioned [21–26]. NSTEMI was defined as patients presenting with chest pain suggestive of myocardial ischemia, with positive markers of myocardial damage (creatinine kinase-MB or troponin) and/or electrocardiographic changes other than ST segment elevation. The diagnosis was made at the time of admission to the cardiac intensive care unit. Patients with ST-segment elevation, new onset left bundle branch block, cardiac arrest, and those not undergoing coronary angiography during the hospitalization were excluded.

We included only patients undergoing angiography, in order to capture patients who had definite acute coronary syndrome and coronary artery disease. Fasting lipid profiles including total, LDL, high-density lipoprotein (HDL) cholesterol and triglycerides that were measured in the first 24 hours of admission were collected. Clinical variables, angiographic results, and outcomes were obtained from electronic and written medical records, cardiac catheterization laboratory data forms, and the CICU database. The CICU database is a prospective registry of every admission to the 16-bed CICU. The database includes 300 distinct data elements prospectively recorded on case report forms by trained research assistants and updated annually. Six-month clinical outcomes were collected using chart review. All-cause mortality data was verified with the Social Security Death Certificate Registries with three-year follow-up.

Patients were divided into two groups according to whether they had TG level below or above the median TG. The primary endpoint was three-year all-cause mortality. The secondary endpoint was MACE at six months. MACE was defined as all-cause mortality, non-fatal myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) at follow-up.

Statistical analysis

Baseline demographic and clinical characteristics were compared between groups using Student's t-test for continuous variables and χ^2 test/Fischer Exact Test for categorical variables. Cox proportional hazard analysis was used to determine the independent predictors of all-cause mortality. In addition, adjusted survival curves were constructed and compared with Cox-regression survival analysis. Adjustment was done for both baseline variables with unequal distribution (gender, race, prior myocardial infarction, hypertension, diabetes, lipid-lowering therapy, prior aspirin, beta-blockers, diastolic blood pressure, and admission HDL level). A p-value ≤ 0.05 was considered significant for all analyses. Statistical analysis was done using SPSS 11.5.

Table 1. Baseline characteristics.

Variable	TG ≤ 200 mg/dL (n = 395)	TG > 200 mg/dL (n = 124)	P
Mean age ± SD	64 ± 12	59 ± 12	0.02
White	229 (58%)	92 (74%)	0.008
Female	156 (40%)	54 (44%)	0.40
Previous MI	116 (29%)	36 (29%)	1.00
CHF	45 (11%)	20 (16%)	0.20
Diabetes	118 (30%)	52 (42%)	0.01
Hypertension	257 (65%)	88 (71%)	0.20
Prior PCI	48 (12%)	34 (27%)	< 0.001
Aspirin	158 (40%)	56 (45%)	0.31
Beta-blockers	120 (30%)	58 (47%)	0.001
Lipid-lowering medications	99 (28%)	42 (39%)	0.03
Intra-aortic balloon pump	19 (5%)	8 (7%)	0.47
Mechanical ventilation	21 (5%)	4 (3%)	0.42
PCI	210 (53%)	72 (58%)	0.33
CABG	44 (11%)	22 (17%)	0.054
LVEF:			0.033
Normal	210 (51%)	64 (52%)	
Mildly depressed	74 (19%)	36 (29%)	
Moderately depressed	76 (19%)	16 (13%)	
Severely depressed	43 (10%)	8 (6%)	
CAD stenosis:			0.40
Non obstructive	388 (10%)	7 (6%)	
One vessel disease	122 (31%)	34 (24%)	
Two vessel disease	93 (24%)	31 (24%)	
Three vessel disease	142 (36%)	51 (41%)	

TG — triglyceride; MI — myocardial infarction; CHF — congestive heart failure; PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft surgery; LVEF — left ventricular ejection fraction at the time of angiography; CAD — coronary artery disease

Results

Between the beginning of 1997 and the end of 2000, of the 836 patients admitted with a diagnosis of NSTEMI, 517 had fasting lipid profiles measured within 24 hours of admission. The median TG level was 200 mg/dL, and 395 (76%) patients had TG ≤ 200 mg/dL and 124 (24%) patients had TG > 200 mg/dL.

Table 1 compares the baseline and demographic characteristics of the two groups. Patients with low TG were more often Caucasian, but there was no statistically significant difference in gender between the two groups. The low TG patients were less often on lipid-lowering therapy, acetylsalicylic acid or beta-blockers. Also, they less often had a prior history of hypertension or diabetes mellitus. There was no significant difference noted in the rate of intra-aortic balloon pump use or mechanical ventilation use between the two groups.

All patients included in this analysis underwent coronary angiography. There were no significant differences in the severity of coronary artery disease between the two groups. Left ventricular (LV) function estimates with either ventriculography or echocardiography were also obtained for all patients. The degree of LV dysfunction between the two groups was significantly different, with more patients in the low TG group having moderately to severely depressed LV function. In addition, revascularization therapy with PCI was not different between the two groups; however the rates of CABG were significantly lower in patients with TG ≤ 200 mg/dL i.e. 11% *vs* 17% with a p value of 0.054 (Table 1).

The mean admission lipid profile and peak cardiac enzymes between the two groups are shown in Table 2. Patients who had admission TG ≤ 200 mg/dL had higher mean HDL cholesterol levels, but the mean LDL levels were comparable. Infarct sizes as estimated by peak creatinine kinase levels were comparable between the two groups, but were significantly different when estimated by troponin levels, with higher levels seen in the low TG group.

Table 2. Admission lipid profile and peak cardiac enzymes.

Variable	TG ≤ 200 mg/dL (n = 395)	TG > 200 mg/dL (n = 124)	P
Total cholesterol [mg/dL]	178 ± 47	207 ± 56	< 0.001
LDL cholesterol [mg/dL]	110 ± 41	110 ± 51	0.9
HDL cholesterol [mg/dL]	46 ± 14	37 ± 10	0.03
Peak creatine phosphokinase [mg/dL]	81 ± 122	62 ± 102	0.12
Peak troponin [ng/dL]	95 ± 145	64 ± 114	0.031

Table 3. Six-month outcomes.

Variable	TG ≤ 200 mg/dL (n = 395)	TG > 200 mg/dL (n = 124)	P
Death (%)	34 (9%)	4 (3%)	0.045
MACE (%)	93 (24%)	24 (19%)	0.33
MI (%)	19 (7%)	6 (4%)	0.41
CABG (%)	9 (2%)	2 (2%)	1.00
PCI (%)	10 (5%)	8 (7%)	0.55

MACE — major adverse cardiac event; MI — myocardial infarction; CABG — coronary artery bypass graft surgery; PCI — percutaneous coronary intervention;

Table 4. Independent predictors of all-cause mortality.

Variable	Hazard ratio	95% confidence interval	P
Diabetes	3.2	1.9–5.8	< 0.0001
Troponin elevation (per 1 mg/dL)	1.002	1.001–1.003	0.029
Triglycerides ≤ 200 mg/dL	2.5	1.04–5.9	0.047
Age > 65 years	2.5	1.5–4.2	< 0.0001

Adjusted for gender, race, and prior myocardial infarction, hypertension, lipid-lowering therapy, prior aspirin and beta-blocker, diastolic blood pressure and admission HDL level

There were no significant differences in MACE between the two groups at six months, as shown in Table 3. However, patients with TG ≤ 200 mg/dL had a statistically significant higher all-cause mortality at six months (9% *vs* 3%, p = 0.045). At three years, patients with admission TG ≤ 200 mg/dL still had a higher all-cause mortality rate compared to patients with TG > 200 mg/dL (13.4% *vs* 5.6%, p = = 0.016, odds ratio [OR] 2.6, 95% confidence interval [CI] 1.2–5.8). This continued to be significant, even after adjusting for gender, race, prior myocardial infarction, hypertension, diabetes, diastolic blood pressure, admission HDL levels, use of lipid-lowering therapy, prior aspirin and beta-blocker use (OR 2.5, 95% CI 1.04–5.9, p = 0.04). The independent predictors of all-cause mortality are shown in Table 4. Adjusted three-year mortality curves are shown in Figure 1.

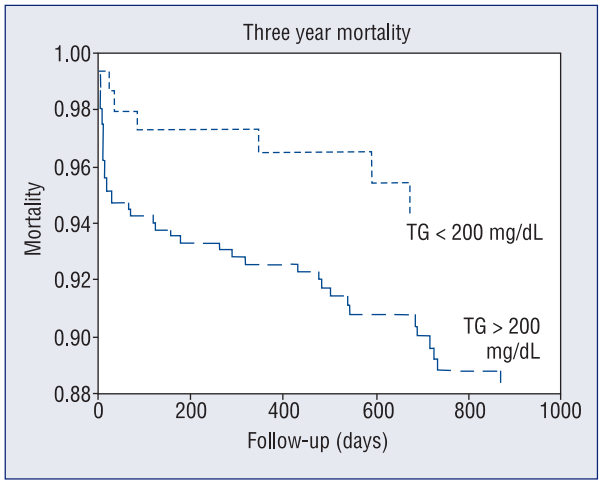

Figure 1. Kaplan-Meier curve showing mortality for patients with low triglyceride (TG) *versus* that for patients with high TG over a period of three years.

Discussion

This analysis demonstrates that a TG level of ≤ 200 mg/dL obtained within 24 hours of admission is associated with higher long-term all-cause mortality in patients admitted with NSTEMI.

To the best of our knowledge, this is the first study to report this observation in acute coronary syndrome patients. This finding initially appears to contradict current thinking about lipids and outcome in patients with CAD. Elevated cholesterol and TG levels have been shown to increase the risk of atherosclerotic heart disease and its complications, while lipid lowering has been shown to reduce adverse cardiovascular events [6–14]. Hypertriglyceridemia has been shown to be an independent risk factor for major cardiac events, even after controlling for cholesterol levels [1–5]. Hypertriglyceridemia combined with elevated cholesterol levels further increases the risk of cardiac events by approximately 600% [27].

However, it is possible that lower triglyceride level at the time of a myocardial infarction in this patient population may actually identify patients with higher long-term all-cause mortality. The two populations of low and high TG patients are inherently different. Although we used Cox analysis and attempted to account for all known different characteristics between the two groups, there could have been some other variables that we did not account for that could have resulted in this worse long term outcome.

Another explanation for our findings could be differences in the atherosclerotic disease pattern. Atherosclerotic complication such as an myocardial infarction is usually a result of multiple factors, and lipid level is only one of the identified risk factors. In fact, it has been recently shown that the level of an inflammatory marker C-reactive protein be a better predictor of worse outcome than reduction in lipid levels after NSTEMI [28]. Seventy five percent of the events are still not prevented by aggressive treatment with statins to achieve LDL cholesterol levels to ≤ 70 mg/dL [10]. Therefore, there are other factors than TG levels that confer this risk in most patients. It is possible that patients who have a myocardial infarction in spite of a low TG level have other risk factors that are not readily modifiable. Thus, plaque rupture in the setting of a low TG level may signify more complex atherosclerotic disease in patients with a higher risk of long-term events.

An example of a preventative measure that may be a marker of adverse prognosis at the time of an event is aspirin therapy. Aspirin use is known to reduce atherothrombotic complications in patients with cardiovascular risk factors [29]. However, aspirin use within the seven days prior to an myocardial infarction has been shown to be an adverse prognosticator in patients with acute coronary syndrome [30]. It is believed that if atherothrombosis develops in spite of aspirin use, this is an indicator of a more complex plaque morphology, conferring higher clinical risk in these patients.

Epidemiological studies have also shown that a lower cholesterol level in general is associated with worse outcome in patients with established heart failure [31, 32]. The reason for this is not entirely clear [33]. Similar findings regarding the association of low serum cholesterol and poor outcome have been reported for elderly individuals [34, 35] and end-stage renal failure patients undergoing hemodialysis [36, 37]. Not much data is available on the harmful effects of specifically low TG. Low TG has been associated with poor outcomes for stroke patients [19, 38].

Decreased LDL levels associated with an increase in TG levels are often seen within a few days of myocardial infarction [39]. However, in our study, lipid levels were drawn within 24 hours of admission rather than within a few days, and most patients had a low TG level (76%), with comparable LDL levels between the two groups to explain the difference in mortality observed at three years. It is possible that low TG may be associated with illnesses other than cardiovascular disease that lead to higher all-cause mortality.

Hypertriglyceridemia has been shown to be the commonest cause of low HDL cholesterol levels [40]. However, in our study, the group with low TG had a higher HDL level than the group with high TG. Also the group with low TG contained a lower percentage of people with a history of congestive heart failure, diabetes mellitus, hypertension or PCI in their history. However, multivariate analysis adjusted for all the above confounding variables was still associated with higher three-year all-cause mortality in patients with TG ≤ 200 mg/dL.

Another possibility is the fact that patients with lower TG at baseline do not get as aggressively treated with lipid-lowering therapy. Similar trends were seen in this study, with fewer patients being on lipid-lowering therapy in the low TG group. This could account for less aggressive follow-up and risk factor modification in this group of people. Since follow-up treatment data is not available, this cannot be ruled out from the current analysis.

The results of our study accord with the results of an earlier study on a similar cohort of patients. That showed that low LDL cholesterol at the time

of admission was associated with higher all-cause three year mortality [20]. The earlier study demonstrated that patients in the low admission LDL study group did not have a significant difference in the infarct size as determined by troponin levels, neither was there a significant difference in the LV dysfunction between the low and high admission LDL groups. This is in contrast to our current study findings of a significantly higher number of patients having a larger infarct size as determined by troponin levels and moderate to severe LV dysfunction in the low TG group as compared to the high TG group. This potentially signifies a different underlying mechanism of action for TG than for LDL in acute coronary syndrome patients that merits further investigation.

Nonetheless, our finding that low TG at the time of admission may be a marker for worse long--term outcome in NSTEMI patients is the first of its kind. The incidence of NSTEMI is growing and it affects more than 1.5 million patients annually in the United States [41]. Measurement of TG on admission in these patients may have significant long--term prognostic implications. Instead of developing a false sense of security in patients with lower TG, these patients may in fact need more aggressive risk modification with lipid-lowering therapy, anti-platelet agents, beta-blockers, ACE inhibitors, smoking cessation and activity modification.

Limitations of the study

The retrospective study design, selection bias, treatment bias and unequal distribution of baseline co-morbidities are the major limitations of our study. We attempted to adjust for the baseline confounding variables with multivariate analysis, but may not be able to account for all confounding variables and physician/treatment effects. The effect of myocardial infarction on the admission lipid profile in the first 24 hours post-admission is not very well understood. Including only those patients with NSTEMI who underwent cardiac catheterization could have limited the external validity of our findings. In addition, therapy for the groups at follow-up was not available and its effect on outcomes is unclear.

Conclusions

Most patients had a TG level ≤ 200 mg/dL at the time of their NSTEMI. Patients with low TG level at the time of their myocardial infarction had higher long-term mortality at three years. The higher mortality persisted after adjusting for baseline differences. Whether atherosclerotic plaque rupture in the setting of low serum TG may be a marker of more complex atherosclerotic disease that portends a worse long-term prognosis in patients with NSTEMI needs to be further explored.

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