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Low Serum LDL Cholesterol Levels and the Risk of Fever, Sepsis, and Malignancy

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Abstract. Lipid lowering therapy of serum LDL cholesterol (LDL) has proved beneficial in reducing cardiovascular morbidity and mortality. Lately the recommended target LDL level in very high risk patients was reduced to <70 mg/dl, raising the question of what the price of such a low level will be. To elucidate this concern, we investigated the associations of low serum LDL cholesterol levels (≤70 mg/dl) and the incidences of fever, sepsis, and malignancy. Retrospective analysis of 203 patients' charts was carried out. Patients were divided into 2 groups: Group 1 (n = 79) had serum LDL levels ≤70 mg/dl, while Group 2 (n = 124) had levels >70 mg/dl. The first group demonstrated increased odds of hematological cancer by more than 15-fold (OR 15.7, 95% CI 1.78-138.4, p = 0.01). Each 1 mg/dl increase in LDL was associated with a relative reduction of 2.4% in the odds of hematological cancer (OR 0.976, 95% CI 0.956-0.997, p = 0.026). Low LDL levels also increased the odds of fever and sepsis between the groups (OR 5.3, 95% CI 1.8-15.7, p = 0.02). In summary, low serum LDL cholesterol level was associated with increased risks of hematological cancer, fever, and sepsis.

Keywords: LDL cholesterol, malignancy, sepsis, oxidized LDL

Introduction

Lipid lowering therapy with statins reduces the risk of cardiovascular events; however the optimal level of low density lipoprotein cholesterol (LDL) is unclear [1]. In 2004 the Coordinating Committee of the National Cholesterol Education Program (NCEP) recommended an optional goal for reduction of LDL level to <70mg/dl in very high risk patients [2]. Intriguingly, some studies on statin therapy for intensive lipid lowering showed no significant reduction in all-cause mortality [1]. Moreover, during the past few years large scale randomized trials and observational studies of lipid lowering agents suggested uncertainty about their beneficial effects with respect to noncardiac mortality and major morbidity [3-10]. The explanation for an increased non-cardiac mortality rate is not clear. A possible mechanism might involve the association between LDL and sepsis/infection/inflammation. Characteristically, though plasma LDL levels are reduced during infection and inflammation, the level of small dense LDL particles, which is sensitive to oxidative damage, is increased [11]. These modified LDL particles have direct cytotoxic effects, and their accumulation in macrophages stimulates the release of potent inflammatory and prothrombotic mediators that could perpetuate the cycle of inflammation [12,13]. Support for this concept comes from studies in which LDL receptor-deficient (LD) mice with increased circulating LDL levels were protected against the lethal effects of endotoxemia and Gram-negative infection [14]. In patients who required intensive care for more than 7 days and who were randomly assigned to either conventional or intensive insulin therapy, it was the lipid (increased

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levels of HDL and LDL) rather than the glucose control that independently determined the beneficial treatment effects of intensive insulin therapy on morbidity and mortality [15]. These observations are consistent with the fact that LDL and HDL are the predominant lipopolysaccharide-binding lipoproteins in patients with sepsis, and thus may play crucial roles in attenuating sepsis-related LPS damage [15].

We undertook this study in order to investigate whether the currently recommended low LDL levels of ≤70 mg/dl might pose an increased risk of infection for patients.

Materials and Methods

A retrospective analysis was performed of 1000 consecutive medical records of patients hospitalized at the Wolfson Medical Centre during a period of one yr (January to Deceember 2005). Patients' files were divided into 2 groups on the basis of serum LDL levels: patients with serum LDL levels ≤70 mg/dl (Group 1), and patients with serum LDL levels >70mg/dl (Group 2).

The medical history was extracted from each patient's chart, including: age, sex, number of hospitalizations during 2005, chronic background illnesses (ischemic heart disease, diabetes, hypertension, malignancy, etc.), and the medications prescribed (with emphasis on HMG CoA reductase inhibitors). The primary reason for each patient's latest hospitalization was recorded and categorized as: I, Fever; II, Sepsis; or III, Neither fever nor sepsis.

Sepsis was defined according to the ACCP/SCCM Consensus Conference definitions [16]. Fever was defined as an oral temperature of ≥38°C or a rectal temperature of ≥38.3°C. Survival or death of each patient was recorded at the last hospital day.

Laboratory data were extracted from each patient's chart and included: complete blood count, serum urea, creatinine, electrolytes, albumin, liver function tests, cholesterol, triglycerides, HDL, calculated LDL, and blood gases.

Analysis of data was carried out using SPSS 9.0 statistical analysis software (SPSS Inc., Chicago, IL, USA). For continuous variables, such as age and laboratory parameters, descriptive statistics were calculated and reported as mean ± SD. Normalcy of distribution of continuous variables was assessed using the Kolmogorov-Smirnov test (cut-off at p = 0.01). Continuous variables were compared by LDL category using the t-test for independent samples.

Categorical variables (eg, sex and co-morbid conditions) were described using frequency distributions and are presented as percentages. The Chi-square test was used to compare categorical variables by group. Outcomes including death and tumors were modeled using logistic regression analysis. All tests are two-sided and considered significant at p <0.05.

Results

The charts of 203 patient were selected. A total of 79 patients had serum LDL levels ≤70 mg/dl (Group 1), and 124 patients had serum LDL levels >70 mg/dl (Group 2).

Table 1 displays the patients' characteristics. There were significantly more males in group 1, 56 (70.9%) vs 52 (41.9%), p = 0.001. Furthermore, Group 1 patients had significantly more days of hospitalization (15.5 ± 31.7 vs 6.6 ± 9.8 days, p = 0.018). A greater proportion of Group 1 patients had a history of MI [22 (27.8%) vs 17 (13.7%), p = 0.013], PTCA [22 (27.8%) vs 18 (14.5%) p = 0.02], CABG [10 (12.7%) vs 3 (2.4%), p = 0.004], and AF [16 (20.3%) vs 9 (7.4%), p = 0.006]. A marginally smaller proportion of Group 1 patients was hypertensive [30 (38%) vs 63 (50.8%), p = 0.074].

Laboratory results for both groups are shown in Table 2. WBC (16.2 ± 22.7 vs 10.2 ± 9.6 $x10^3$/µl, p = 0.028), serum urea (77.8 ± 53.6 vs 43 ± 30.8 mg/dl, p = 0.0001), and creatinine (1.8 ± 2.0 vs 1.1 ± 0.6 mg/dl, p = 0.002) were significantly higher while platelet count (197.6 ± 151.2 vs 283.9 ± 95.6 $x10^3$/µl, p = 0.032) and serum albumin (2.7 ± 0.7 vs 4.1 ± 0.4 g/dl, p = 0.002) were significantly lower in Group 1 compared to Group 2.

Lipid profiles for both groups are shown in Table 3. As can be seen, LDL (44.5 ± 16.2 vs 127.6 ± 48.9 mg/dl, p <0.0001), HDL (18.9 ± 14.3 vs 59.3 ± 28.19 mg/dl, p <0.0001), and total cholesterol levels (97.4 ± 32.9 vs 210.6 ± 63.69 mg/dl, p <0.0001) were significantly lower in Group 1 compared to Group 2.

In a multivariate logistic regression model controlling for age, sex, MI, HDL, TG, and statin use, LDL ≤70 mg/dl was not associated with death (p = 0.43), carcinoma of the liver, or other solid tumors. However, low LDL levels increased the odds for hematologic cancer by more than 15-fold (OR 15.7, 95% CI 1.78-138.4, p = 0.01). Each 1 mg/dl increase in LDL was accompanied by a relative 2.4% reduction in the odds of hematological cancer (OR 0.976, 95% CI 0.956-0.997, p = 0.026).

Low LDL (Group 1) was also significantly associated with fever/sepsis. Patients in Group 1 had a relative increase in the odds of fever/sepsis

Table 1. Demographic data and background illnesses of patients.

	Group 1 (LDL ≤70 mg/dl) N = 79	Group 2 (LDL >70 mg/dl) N = 124	p
Male gender	56 (70.9%)	52 (41.9%)	0.001
Age (yr)	68.4±18.1	65.6±17.6	0.26
Diabetes mellitus (DM)	20 (25.3%)	32 (25.8%)	0.94
Hypertension (HTN)	30 (38%)	63 (50.8%)	0.074
Myocardial infarction (MI)	22 (27.8%)	17 (13.7%)	0.013
Angina pectoris (AP)	23 (29.1%)	29 (23.4%)	0.362
Percutaneous transluminal coronary angioplasty (PTCA)	22 (27.8%)	18 (14.5%)	0.020
Coronary artery bypass graft (CABG)	10 (12.7%)	3 (2.4%)	0.004
Atrial fibrillation (AF)	16 (20.5%)	9 (7.4%)	0.006
Cirrhosis	2 (2.5%)	2 (1.6%)	0.646
Length of hospitalization days, (± SD)	15.5±31.7	6.6±9.8	0.018
Number of admissions during 2005 (± SD)	2.2±1.3	2.1±1.8	0.795

Table 2. Laboratory values of the patients.

	Group 1 (LDL ≤70 mg/dl) N = 79	Group 2 (LDL >70 mg/dl) N = 124	p
Urea (mg/dl)	77.8±53.6	43.0±30.8	0.0001
Creatinine (mg/dl)	1.8±2.0	1.1±0.6	0.002
Na (mmol/L)	139.3±7.5	136.9±16.2	0.219
K (mmol/L)	4.7±3.9	4.2±0.6	0.194
Uric acid (mg/dl)	6.8±3.4	10.6±4.7	0.980
Albumin (g/dl)	2.7±0.7	4.1±0.4	0.002
Glucose (mg/dl)	132±56.5	138±68.7	0.544
Inorganic P (mg/dl)	3.5±1.5	4.5±0.6	0.129
Alkaline Phosphatase (U/L)	153.8±158.6	109.4±123.4	0.037
Aspartate aminotransferase (AST) (U/L)	88.2±217.0	52.5±107.9	0.121
Alanine aminotransferase (ALT) (U/L)	91.2±348.3	47.0±137.9	0.207
Lactate dehydrogenase (LDH) (U/L)	768.7±1360.9	632.7±1103	0.436
Total bilirubin (mg/dl)	7.5±6.9	9.2±7.5	0.624
White blood count ($x10^3/\mu l$}	16.2±22.7	10.2±9.6	0.028
Hemoglobin (g/dl)	10.5±2.3	13.7±10.3	0.07
Platelets ($x10^3/\mu l$)	197.6±151.2	238.9±95.6	0.032

Table 3. Serum lipid profiles of the patients.

	Group 1 (LDL ≤70 mg/dl) N = 79	Group 2 (LDL >70 mg/dl) N = 124	p
HDL cholesterol (mg/dl)	18.9±14.3	59.3±28.1	>0.001
LDL cholesterol (mg/dl)	44.5±16.2	127.6±48.9	>0.0001
Total cholesterol (mg/dl)	97.4±32.9	210.6±63.6	>0.0001
Triglycerides (TG) (mg/dl)	170.3±113.2	150.4±153.9	0.325

compared to patients with LDL >70 mg/dl (OR 5.3, 95% CI 1.8-15.7, p = 0.002). Each 1 mg/dl increase in LDL was associated with a 2.5% relative decrease in odds of fever/sepsis (OR 0.975, 95% CI 0.96-0.99, p = 0.005).

Discussion

The most interesting findings in this study were that low LDL levels (≤70 mg/dl) were associated with an increased risk of hematological cancer, and that each 1 mg/dl increase in LDL was accompanied by a relative 2.4% reduction in odds of hematological cancer. Further, low serum LDL (Group 1) conferred a relative increase in odds of fever/sepsis. Each 1 mg/dL increase in LDL was associated with a 2.5% relative decrease in odds of fever/sepsis. These results are intriguing and deserve an explanation. Similar observations can be found in other researches as well: for example, in 1992 an elevated risk of total cancer deaths was reported in men with total cholesterol levels <160 mg/dl as compared to 160-190 mg/dl [8]. LDL levels were not reported in that study. LaRosa et al [3] reported 158 noncardiovascular deaths in the group of patients receiving 80 mg/day of Atorvastatin compared to 127 deaths in the group that received 10 mg/day of the drug (OR, 1.25, 95% CI 0.99-1.57, p = 0.06) [3]. Cancers (mainly lung and gastrointestinal) accounted for more than half of the deaths from noncardiovascular causes in both groups, while the remaining deaths were caused by hemorrhagic stroke, infection, degenerative diseases, and metabolic abnormalities other than cancer. There was no difference between the 2 treatment groups in overall mortality.

On the other hand, a meta-analysis of 14 randomized trials of statins (which did not include recent studies with intensive LDL lowering policy) found a 12% relative reduction in all-cause mortality per mmol/L reduction in LDL, which reflected a 19% reduction in coronary mortality accompanied by a non-significant reduction in non-coronary vascular mortality [17]. Another study also did not show any evidence of increased risk of death from cancer or respiratory disease associated with LDL reduction [10]. In a 10-yr follow up of the Scandinavian simvastatin survival study, no difference was observed in the incidence of, or the mortality from, cancer [18].

The issue was brought to the spotlight again by Alsheikh-Ali et al [19] in a recent meta-analysis that assessed the relationship between the magnitude of LDL lowering and cancer. In this article significant inverse association between cancer incidence and achieved LDL levels (R^2 = 0.43, p = 0.009) was demonstrated [19]. The possibility of a pathophysiologic link between decreased LDL levels, infection, and cancer is therefore unclear .

An increasing body of evidence shows a close interplay between lipoprotein metabolism and sepsis [20]. Characteristically, sepsis is associated with a decrease in plasma LDL levels caused partially by TNFα degradation of LDL [20,21]. In parallel, there is an increase of oxidized LDL. These modified particles, which produce direct cytotoxic effects, accumulate in macrophages and stimulate the release of inflammatory and prothrombotic mediators, perpetuating sepsis [12,13].

LDL and HDL are the predominant lipopolysaccharide-binding proteins in patients with sepsis [15], primarily through the interaction of LPS-binding protein (LBP) with LDL and HDL. It is therefore not surprising that LDL receptor-deficient mice, with increased circulating LDL serum levels, were protected against the lethal effects of endotoxemic and Gram-negative infections [14]. These associations suggest a cyclic pattern in which low LDL levels lead to reduced LPS binding, which increases the risk of infection, leading to increased risk of sepsis, more oxidation of LDL, and more inflammation.

Another possible link between low LDL and infection involves LDL's role as a carrier of exogenous coenzyme Q10 (CoQ). CoQ has been shown to be an effective agent for reducing the deleterious effects of septic shock by acting as a free radical scavenger (which stabilizes mitochondrial membranes), and by inhibiting arachidonic acid metabolic pathways, including the formation of various prostaglandins [22]. CoQ also inhibits superoxide production by PMN in endotoxemic shock [23]. Several studies have reported that statins decrease not only LDL levels but also CoQ concentrations in blood [24-26]. This could have a

deleterious effect in patients with sepsis, considering CoQ's roles mentioned above. None of the patients in our study received supplemental CoQ, and we have no measurement of its serum levels in our patients. On the other hand, statin's role in sepsis was also evaluated by Chua et al [27], who performed a systematic review of the literature. Their conclusions support an association between statin use and lower incidence of sepsis and sepsis-related mortality. However, a causal relationship between statin use and reduced sepsis-related mortality was not established [27].

These pathophysiological mechanisms could theoretically contribute to an increased risk of malignancy in our patients, since reactive oxygen species are postulated to be involved in neoplastic transformation. The antioxidant defense system limits cell injury induced by reactive oxygen species [28]. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species and cellular antioxidant capacity. This stress causes mutagenesis, cytotoxicity, and changes in gene expression that initiate or promote carcinogenesis [28-31]. Superoxide dismutase (SOD), which is one of the first-line defense antioxidants, acts as an antiproliferative and anticarcinogenic agent, inhibiting the initiation and promotion of carcinogenesis [31]. Antioxidant vitamins such as vitamin A, E, and CoQ also have a number of biological activities such as alteration of metabolic activation of carcinogens. They can prevent genetic changes by inhibiting DNA damage induced by reactive oxygen metabolites [31]. It could therefore be postulated that low LDL levels might increase the risk of a neoplastic transformation by providing less CoQ to the circulation, thus diminishing the body's total cellular antioxidant capacity.

Lipid-lowering therapy with statins, which on the one hand increases LDL's antioxidant capacity, could on the other hand confer harm by decreasing CoQ levels [21,22]. It is premature to imply causality between LDL levels and sepsis/malignancy, based on our study alone, since the LDL levels could be merely reflecting the severity of the patient's basic condition (eg, as an acute phase reactant). However, the importance of the issue necessitates further studies to clarify the matter.

In conclusion, in our study, decreased LDL levels (≤70mg/dl) were associated with increased risks of hematological cancer, fever, and sepsis.

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