

## Comparison of Lipid Profile in Septic and Non-Septic Patients

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### Abstract

**Background:** The nature of changes in the lipid profile caused by an acute infection is controversial.

**Objective:** In this study we compared concentrations of plasma lipids in 70 septic and non-septic patients in ICU and studied the prognostic impact of cholesterol, LDL-C, HDL-C and triglyceride.

**Methods:** From March 2009 to February 2010, all patients consecutively admitted to the Intensive Care Units of Rasoul Akram University Hospital, Tehran, Iran, were studied. Each person was examined for signs and symptoms of infection during hospital stay. Patients were classified as suffering from sepsis or not at the first 24 hours of admission. Descriptive results of continuous variables were expressed as mean ( $\pm$ SD). The associations between factors were analyzed by t-test and between factors and prognosis by  $\chi^2$  test when appropriate.

**Results:** The study population included 28 males and 42 females with mean ( $\pm$  standard deviation) age of years  $73.6 \pm 15.7$  that 29 of them were in sepsis group and 41 of them in non-sepsis group.

There wasn't any relationship between sex and mortality ( $p=0.34$ ), although by increasing age mortality leveled out ( $r=-0.58$ ,  $p=0.04$ ). The concentrations of total cholesterol ( $89.3 \pm 33.6$  vs  $100.7 \pm 25.3$  mg/dl), HDL ( $20 \pm 5.6$  vs  $30.2 \pm 8.7$  mg/dl), and LDL ( $61.5 \pm 18.7$  vs  $70.6 \pm 14.5$  mg/dl) showed significantly lower values in septic group but no difference could be found in triglyceride level ( $177.7 \pm 28.7$  vs  $182.8 \pm 45.9$  mg/dl). In septic group the initial and second levels of cholesterol were considerably higher in patients who died than those who survived ( $101.6 \pm 37.5$  versus  $69.4 \pm 8.3$  and  $103.2 \pm 23.4$  versus  $79.4 \pm 47$  respectively,  $p=0.00$ ).

**Conclusion:** In ICU setting, measurement of cholesterol values has been shown to improve risk prediction, and inclusion of lipid values in clinical risk assessment scores of critically ill patients has been advocated. Further understanding of the alterations in lipid metabolism may have therapeutic implications in treatment of sepsis.

**Key words:** Lipid; Sepsis; Triglyceride; Cholesterol

## Introduction

Changes in plasma lipid profiles, particularly low levels of high-density lipoproteins (HDL), are associated with several inflammatory and immune diseases in addition to atherosclerosis, including rheumatoid arthritis (1), systemic lupus erythematosus (2), Sjogren's syndrome (3), and ankylosing spondylitis (4).

Systemic inflammation and sepsis are accompanied by severe metabolic alterations, including insulin resistance together with increased levels of triglycerides (TGs) and decreases in high and low-density lipoproteins (LDL) (5).

Clinical studies have clearly established a link between lipid metabolism and systemic inflammation (6, 7, 8, 9).

The mechanisms proposed for sepsis-associated hyperlipidemia include tissue lipoprotein lipase inhibition and up-regulated hepatic triglyceride production (9). Lipoproteins were shown to neutralize lipopolysaccharide (LPS) and exert direct anti-inflammatory actions. HDL and LDL are thus thought to be important regulators of the host immune response during endotoxemia, which may also have the improving potential to care patients with gram-negative sepsis (5).

part from that, reverse cholesterol transport is known to be an important mechanism allowing HDL to prevent the accumulation of cholesterol in leukocytes and the formation of foam cells in the intima of vessel walls (10, 11). Recent studies, however, have suggested that HDL causes a variety of anti-atherogenic or anti-inflammatory actions independent of changes in cholesterol metabolism (10, 12).

Leukocyte adhesion to endothelial cells and subsequent transmigration into the subendothelial space or outside the vascular system are commonly observed at early stages of inflammatory diseases and are thought to be critical in their initiation and progression (10, 12, 13). HDL has been shown to induce the inhibition of the adhesion of leukocytes to endothelial cells and their transmigration, the inhibition of proinflammatory gene expression in endothelial cells, and the activation of endothelial NO

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synthase (eNOS) (10, 12, 14). Furthermore, HDL protects normal endothelial cell functions by inhibiting apoptosis and stimulating re-endothelialization after injury (14). On the other hand, whether in patients with less severe systemic infections plasma lipids have prognostic implications, or could help to differentiate bacterial from nonbacterial infection, remains unknown.

Using drugs not only to bring the plasma lipid profile to normal levels by lowering plasma LDL cholesterol and/or increasing plasma HDL cholesterol but also to enhance the ability of HDL to stimulate cholesterol metabolism-independent anti-inflammatory actions may be an effective way to protect against and treat inflammatory diseases (15). So, nutritional lipids supplied during critical illness have been shown to modulate the host response to inflammation (5). Thus, further understanding of the alterations in lipid metabolism may have therapeutic implications in treatment of sepsis with specific compounds that manipulate lipid profiles, such as fibrates, statins, niacin and even reconstituted HDL.

In this study we compared concentration of plasma lipids in 70 septic and non-septic patients in ICU and studied the prognostic impact of total cholesterol (TC), LDL-C, HDL-C and TG.

### Material and Methods

**Patients:** From March 2009 to February 2010, all patients consecutively admitted to the Intensive Care Units (medical and surgical) of Rasoul-Akram University Hospital, Tehran, Iran, were considered for the study. Each person was examined for signs and Symptoms of infection during hospital stay. Patients who admitted with trauma or after surgery to ICU were excluded. Patients were classified by two intensivists—according to their clinical and laboratory data as suffering from sepsis (group A) or not (group B) at the first 24 hours of admission, according to established consensus definitions (16). Upon admission into ICU, the following items were recorded for each patient: age, sex, fasting blood sugar (FBS), TG, TC, HDL and LDL at admission and 10 days later. Length of stay and final outcome were also recorded. The study protocol was approved by the local ethic committee.

Sepsis was defined as Systemic inflammatory response syndrome (SIRS) plus infection (16) and (SIRS) was defined as when patients have more than one of the following clinical findings:

1. Body temperature higher than 38°C or lower than 36°C.
2. Heart rate higher than 90/min.
3. Hyperventilation evidenced by respiratory rate higher than 20/min or PaCO<sub>2</sub> lower than 32 mmHg.
4. White blood cell (WBC) count higher than 12 000 cells/ $\mu$ L or lower than 4000 cells/ $\mu$ L.

**Statistical analysis:** Descriptive results of continuous variables were expressed as mean ( $\pm$ SD). The associations between factors were analyzed by t-test and between factors and prognosis by  $\chi^2$  test when applicable.  $P < 0.05$  was considered significant. Statistical calculation was performed with SPSS statistical software (version 18; SPSS Inc, Chicago, Ill).

### Results

The study population comprised 28 males and 42 females with mean age of  $73.6 \pm 15.7$  years, 29 of whom were in sepsis group and 41 in non-sepsis group. The diagnosis of

the 41 patients with non-sepsis group and most common sites of infection in sepsis group were demonstrated in tables 1 and 2, respectively. Moreover, the demographic data and patients characteristics are shown in Table 3. There was no relationship between sex and mortality ( $p = 0.34$ ), although by increasing age mortality leveled out ( $r = -0.58$ ,  $p = 0.04$ ).

In septic group, the initial and second levels of cholesterol were considerably higher in patients who died than in those who survived ( $101.6 \pm 37.5$  versus  $69.4 \pm 8.3$  and  $103.2 \pm 23.4$  versus  $79.4 \pm 47$  respectively,  $p < 0.001$ ). However, there weren't any differences between patients who died and survived regarding levels of TG, LDL, HD and diabetes mellitus (Table 3).

Table 1- Diagnosis of patients with non-sepsis group

Organ	Number
Central Nervous System	21
Respiratory	6
Multiple Trauma	4
Cardiovascular	4
Gastroenterological	2
Malignant	1
Renal	2
Hematologic	1
Total	41

Table 2- Site of infection in sepsis group

Organ	Number
Respiratory System	12
Urinary Tract	9
Wound Infection	2
Gastrointestinal Infection	1
Cellulitis	1
Unknwon	4
Total	29

Table 3- Clinical and laboratory findings at admission and 10 days later according to the diagnosis

	Sepsis(n=29)	Non-sepsis(n=41)	Pvalue
Male/female	12/17	16/25	0.46
Age(mean $\pm$ SD)y	77.4 $\pm$ 14.1	70.8 $\pm$ 16.3	0.35
Cholesterol-1(mean $\pm$ SD)mg/dl	89.3 $\pm$ 33.6	100.7 $\pm$ 25.	0.11
Cholesterol-2(mean $\pm$ SD) mg/dl	94.1 $\pm$ 21.8	107.8 $\pm$ 23.4	0.00
Triglyceride-1(mean $\pm$ SD) mg/dl	177.7 $\pm$ 28.7	182.8 $\pm$ 45.9	0.93
Triglyceride-2(mean $\pm$ SD) mg/dl	185.7 $\pm$ 40	181.4 $\pm$ 40	0.56
LDL-1(mean $\pm$ SD) mg/dl	61.5 $\pm$ 18.7	70.6 $\pm$ 14.5	0.02
LDL-2(mean $\pm$ SD) mg/dl	62.7 $\pm$ 15.5	69.1 $\pm$ 14.4	0.01
HDL-1(mean $\pm$ SD) mg/dl	20 $\pm$ 5.6	30.2 $\pm$ 8.7	0.00
HDL-2(mean $\pm$ SD) mg/dl	20.7 $\pm$ 6.6	27.2 $\pm$ 10.5	0.00
FBS(mean $\pm$ SD)mg/dl	132.3 $\pm$ 58.1	116.8 $\pm$ 61.3	0.35
Diabetes	20/29	18/41	0.07
ICU stay(mean $\pm$ SD)d	14.8 $\pm$ 5	11.5 $\pm$ 5.7	0.00
mortality	18/29	12/41	0.00

## Discussion

This study investigated changes in plasma lipid levels in patients with sepsis, and particularly whether they have prognostic implications. We found markedly lower levels of cholesterol, LDL and HDL on admission and 10 days later with sepsis. In addition, low cholesterol, but not low HDL, LDL and TG concentrations, was independent predictors of short-term mortality in sepsis. The exact pathophysiological mechanisms underlying hypocholesteremia in severe illness and sepsis have never been fully understood (17). Different mechanisms, including dysbalance between synthesis and utilization of plasma lipids, usage of lipids to restore damaged cell membranes, and interaction of cytokines and bacterial toxins with lipids, have been discussed (17-26). Clinical and experimental studies demonstrated that high circulating levels of cytokines decrease cholesterol levels during severe infection (20, 26). Anti-inflammatory and anti-oxidative properties of HDL were described (18, 24-26). One important mechanism leading to the decrease in HDL is consumption through bacterial substances, particularly lipopolysaccharide (LPS) and other endotoxins. Thus, lipids are used as a scavenger mechanism of host defense because cholesterol and lipoproteins mediate LPS clearance through detoxification, forming complexes and neutralizing its toxic effects (20-23, 27).

In addition, lipoproteins bind a wide variety of enveloped and non-enveloped DNA and RNA viruses and are involved in defense against several parasites (22, 23). In accordance with these experimental findings, the present study demonstrates that in unselected patients with sepsis, less cholesterol values on admission were seen like some other studies (19, 27, 28, 29, 30). If confirmed in further studies and combined with other prognostic clinical and laboratory markers, measurement of plasma lipids may allow clinicians to assess the patients with sepsis. The variation during the hospital stay and the correlation of HDL with albumin and C-reactive protein suggests that HDL is a dynamic surrogate marker of systemic infections (31). Keeping this in mind, physicians should be reminded that measurement of cholesterol values in patients with systemic infections should not be used for cardiovascular risk prediction, since circulating levels of cholesterol, LDL and HDL may be false-low and levels of TG may be false-increased respectively.

This study showed that 69% of 29 patients admitted by sepsis had diabetes mellitus (DM), hence, of any 3 patients with sepsis, 2 are diabetic. The prevalence of DM was first studied by the Institute of Nutrition and Nutritional Sciences during 1976-1977 in Iran. They reported a prevalence of 0.6-5 in 1000 in children and 2-10% in adults. In 1993, Endocrine Research Center and Institute of Nutrition and Nutritional Sciences of Shahid Beheshti Medical University reported a prevalence of 7.2% in >30 years old population of Tehran and 1.4% in >10 years old population of Isfahan (32). Therefore, if the maximum prevalence of DM in general population is considered as 10%, the prevalence of DM in patients with sepsis in our study (69%) will be quite high. Our findings revealed not only the higher prevalence of DM among septic patients but also showed that mortality increased with aging which is in agreement with previous reports

(33-35). This study showed 43% mortality rate with a statistically significant difference between mortality in septic (62%) and non-septic (29%) patients.

In critically ill patients, changes in cholesterol levels, and particularly a decrease in HDL, have been put forward as a predictor of severity of illness and adverse medical outcome by some investigators (17, 18, 28, 36-39), while other studies could not confirm this association (40, 41, 42). In our study of patients with sepsis, we found a significant difference in cholesterol, but not in HDL, LDL and TG, between survivors and non-survivors. Accurate assessment of disease severity and prediction of outcome are prerequisites for safe decision-making on management in patients with sepsis. In ICU setting, measurement of cholesterol values has been shown to improve risk prediction, and inclusion of lipid values in clinical risk assessment scores of critically ill patients has been advocated.

Plausible biological explanations exist to explain these associations, including an interaction of lipoproteins with endotoxin and the regulation of cytokine production. It remains unclear whether these observed alterations in lipid profile are a consequence of the physiological disturbance or whether they have a more causative role, worsening organ dysfunction or predisposing to infection. Lipid emulsions provide a vehicle for drug delivery, have become an important part of nutrition, and are emerging as a therapy for specific intoxications. The nature, dietary source and amount of lipid provided to critically ill patients may be enormously important and warrant more rigorous investigation. Further understanding of the alterations in lipid metabolism may have therapeutic implications in treatment of sepsis with specific compounds that manipulate lipid profiles, such as fibrates, statins, niacin and even reconstituted HDL.

**Conclusion:** In ICU setting, measurement of cholesterol values has been shown to improve risk prediction, and inclusion of lipid values in clinical risk assessment scores of critically ill patients has been advocated. Further understanding of the alterations in lipid metabolism may have therapeutic implications in treatment of sepsis.

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