



**Article Name** 2- **Determination of Association between the Decrease in Cholesterol Concentration and Sepsis in Patients Admitted in the ICU**

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### Introduction

Sepsis remains a major cause of hospital-based mortality and morbidity especially in ICU. Severe sepsis is frequently fatal and expensive. Severe sepsis is defined as sepsis associated with acute organ dysfunction, occurring in more than 700000 patients each year. Despite antibiotic usage and supportive care, there is only a 50% to 70% survival rate. (1) It is estimated that there is 100000 to 500000 episodes of sepsis each year in the United States that involves 25% of patients admitted in ICU and causing 80000 deaths each year (2). Some major variables may create discrepancies in predicting the outcome in critically ill patients. These are for example gender, preinfectious, preoperative immune and or genetic status, age, iatrogenic and nosocomial events. In some studies, it is demonstrated that low circulating cholesterol concentration is associated with a greater mortality rate than others (3). Cholesterol is the basic element of cell membranes and is likely to be essential in extensive tissue repair processes for instance in sepsis or after trauma. Therefore, hypocholesterolemia may be an indicator of the metabolic response seen in stress (4). Because of sepsis survival rate of 70%, we have studied the relationship between serum cholesterol level and sepsis seen in critically ill patients. With regard to the results, we began a nutritional supplement strategy in the ICU in order to provide a positive balance for these patients that decrease the severity and mortality rates of ICU patients. Nevertheless, every where, prevention is always the first aim for reducing the mortality and morbidity rates. In regard to weak therapeutic strategies in our country and a high mortality rate that is expected in Iran, this hypothesis can help to reduce mortality and morbidity rates and provide a less expensive method for the patients.

### Material & Method

Study was conducted in the medical intensive care unit (MICU) of Iran University hospitals including Hazrate Rasool-e-Akram and Firoozgar in a cross-sectional case series design. Patients were totally 52 participants. 26 of them were septic and others were not. The main inclusion criteria for our study were that all of the patients who were septic at the admission time to ICU. The patients were matched for age, sex and duration of hospitalization for case and control groups. The criteria for including the patient into the case group were any patient who had 2 to 4 of the following signs considered as septic: 1-Hypo or Hyperthermia ( $T < 36$  or  $T > 38$  CA? a) 2-Tachycardia (PR  $> 90$  Bpm) 3-Tachypnea (RR  $> 20$  breath per minute) 4-Increased or decreased WBC counts (WBC  $> 12000$  or WBC  $< 4000$ ) The cholesterol level was first measured on admission

to ICU and then twice weekly. Any patient with sepsis criteria transferred to case group. Cholesterol concentration was measured by selectra setting as mg/dl. This method was followed until the appropriate sample size was achieved. All of the information was written on checklists. Results were expressed as means $\pm$ 2SE by SPSS version 10.00. The statistical significance of difference between means was calculated by using paired and pooled t-tests. The correlation was calculated by chi-square. The patients' names, characteristic and financial data were not be disclosed.

## Result

The sample included 52 patients which had been admitted to the ICU of Iran University of Medical Sciences hospitals during the winter of 2002. Patients were divided into two separate groups: a group in which the patients were septic and the other group in which the patients were not septic. The average age of patients was 58.44 ( $\pm$ 5.8) which varied from 5 to 107 years. The median age was 65 and the distribution was normal. The male to female ratio was 0.92, 48.1% of them were male and the rest (51.9%) were female. The average primary cholesterol level was 161 ( $\pm$ 11.4) mg/dl which varied from 68 to 280 mg/dl. Its distribution was normal. The average of the last cholesterol level was 149 ( $\pm$ 14.52) mg/dl that varied from 40 to 328mg/dl. Its distribution was normal. 61.5 % of the patients expired, and 38.5% were discharged from the ICU. In septic patients, 38.4% of them had positive blood culture. The results of blood culture was summarized as following: E. coli: 4% of the patients Klebsiella: 15%of the patients Staphylococcus: 19% of the patients In septic patients, the average time of hospitalization in the ICU was 7.3 ( $\pm$ 1.8) days There were no significant statistical differences between two groups. ( $p=0.537$ ) The average age of septic patients was 60.1 years. There were no significant statistical differences between two groups. The average primary cholesterol level that was measured at the admission time to the ICU in septic patients was 152.3 ( $\pm$ 17.74) mg/dl which varied from 68 to 280 mg/dl. In comparison to the other group there were no significant statistical differences between two groups ( $p=0.692$ ); however, the average of the last cholesterol level in septic patients was 134 ( $\pm$ 28.04) mg/dl which varied from 40 to 326 mg/dl that showed significant differences with the other group. Thus, there were statistically significant correlations between the last cholesterol level and presence of sepsis; ( $p=0.042$ ). However there were no significant correlations between the primary cholesterol level and presence of sepsis. ( $p=0.8$ ) Most of the septic patients expired (88.9%), and only 11.1 %of them were treated. In the non-septic patients, 65% of them were discharged while 35%of them died; So, there were positive correlation between the patients outcome and presence of sepsis. ( $p=0.000$  ) In our study, 11 participants had primary cholesterol level below 130 mg/dl .Of them, 7 patients were in the septic group and 4 patients were in the non-septic, group. There were no significant correlations between the primary cholesterol level and septic status.19 participants had a last cholesterol level that was below 130 mg/dl. Of them, 13 patients had sepsis and others were not septic. So, there were statistical correlations between low cholesterol level and presence of sepsis. ( $p=0.050$  ) In our study, the septic patients were divided into two age groups; below and above 65 years. It was apparent that there were no differences between the patient age group and being septic. ( $p=0.692$  ) In septic patients, the amount of primary and last cholesterol levels were compared in males and females. There were

no significant differences between the cholesterol levels and sex in our study. ( $p > 0.05$ ). Thus, we could demonstrate that there were positive correlations between the patients outcome and cholesterol level ( $p = 0.03$ )

In our study, it was demonstrated that there were significant statistical correlations between the last cholesterol level and presence of sepsis. The association between infectious disease mortality and a low total cholesterol concentration is surprising. Lipoproteins may be important "mops" within the circulation for dealing with endotoxemia, and clinicians should be aware that when severe hypocholesterolemia is evident on hospital admission biochemical profile, serious microbial infection should be suspected. (3) These results suggest that preadipocytes could function as macrophage-like cells and raise the possibility of a potential direct involvement of adipose tissue in inflammatory processes. This link between adipose tissue and immunity is reinforced by the demonstration that adipose tissue may also be a source of factors not related to fat metabolism. Indeed, in both humans and rodents, adipose tissue transcribes high levels of proteins involved in the alternative pathway of complement system such as adipose/factor D, factor C3 and B, and acylation stimulation protein (ASP) together with the proteins that control their expression. Other secreted proteins, such as interleukines and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), a major mediator of inflammation, are secreted by adipocyte and macrophages. In addition, the recently discovered leptin has been shown to be involved in both energy metabolism and proinflammatory immune responses, especially via macrophage activity and T lymphocyte proliferation. These points raise a question about the relationship that could exist between adipocytes and immune cells, especially macrophages, which has led us to compare both cell types. Macrophages could be characterized by specific immunocytochemical staining as well as functional features, including phagocytosis and antimicrobial activity by oxygen dependent or independent mechanisms. (5) Hypocholesterolemia has been observed in many chronic (neoplasia) and acute diseases (burns, trauma, infections, pancreatitis). Total serum hypocholesterolemia is associated with a lower than normal cholesterol content of the low density lipoprotein fraction of serum lipoproteins. Caloric or protein deficiency could be one of the causes of hypocholesterolemia. Nevertheless, malnutrition is probably not the only cause. Experimental data have proved that endotoxins, cytokines, and mediators of inflammation are able to lower cholesterol levels through a different mechanism than malnutrition alone. Furthermore, in some recent studies carried out on elderly subjects, gross malnutrition indices (weight, low lean body mass and low fat mass) did not correlate with hypocholesterolemia, even though it was present. The absence of cholesterol in parenteral nutrition solutions, which are often used in critically ill patients with acute abdominal illness, could be another cause of hypocholesterolemia and intestinal malabsorption. The importance of cholesterol content on cell membrane fluidity and microviscosity could explain the observed correlation between cholesterol and the alternations observed. Indeed, lipid microviscosity affects transmembrane transport phenomena, stimulus transmission, linkage with receptors and enzymatic activities. Cholesterol reduction would lower membrane lipid microviscosity; thus, decreasing the exposure of membrane proteins and reducing membrane functions. Hypocholesterolemia can

be considered as the result of a disequilibrium between cell requirements and cholesterol availability. Cellular growth, which accompanies tissue repair and activated immune defenses increases in conditions of stress, necessitating a greater amount of cholesterol to synthesize new membranes. Increased cholesterol uptake and decreased nutritional intake (malnutrition), together with the possible role of lowered hepatic synthesis, could explain why we observed low cholesterol level. Gui and colleagues showed that in the critically ill surgical patients admitted to the ICU, there was a 38 % frequency of cholesterolemia below 120 mg/dl. In a similar investigation carried out on all the patients admitted to the surgical wards of the same hospital from 1969 to 1991 (7286 patients), 17% prevalence of cholesterolemia < 130 mg/dl has been observed (unpublished data) (4). In our study the prevalence of cholesterolemia < 130 mg/dl in septic patients was 73% showing significant statistical differences with previous study. The cause of this difference could be due to absence of an appropriate nutritional support in our ICUs or because of a hypermetabolic state in the patients. In an experimental study, Netea and colleagues (6) showed that mice deficient in receptors for low density lipoprotein with endogenous hypercholesterolemia, were protected against infections with gram negative microorganisms. Our study has proven it too. Rejection of organ transplants is clearly less likely when patients are treated with cholesterol lowering drugs, which suggests that such drugs may have an immunomodulatory effect. The other study (7), demonstrated that for both men and women of 85 years old and older, high total serum cholesterol concentrations are inversely correlated with low mortality rate, and high cholesterol is associated with increased survival. As compared with participants who had low total cholesterol concentrations, those with moderately high and high concentrations have a lower mortality risk of 22% and 38% respectively; however, this association is not proved in our investigation. It can be due to minimal sample size or other factors that can disturb this correlation. In our study, only 38% of the septic patients had a positive blood culture and the most common organism was gram negative enteric pathogens. There were no differences between our study and references. The presence of only few cases with positive blood culture can be distributed to some factors: 1-The patients had received antibiotics before. 2-The culture plates had not truly been prepared or the time for bacterial growth was not enough. 3-It can be due to presence of SIRS which has not improved to sepsis.

## **Discussion**

### **SUGGESTIONS**

1-Because of the high rate of sepsis, we all should try to limit iatrogenic sources of infection. In particular, it is in our opinion that reducing catheter-related infections is a requisite and must be emphasized. 2-Many epidemiological studies have examined the relation between low concentrations of total serum cholesterol and sepsis risk, but their results are inconsistent; So, the design of some case control studies must be improved. 3-Correction of the hypolipidemia by a reconstituted high density lipoprotein preparation, offers a new strategy for the prevention and treatment of endotoxemia. However, it should be approved by great randomized controlled trials. 4-To determine the cause and effect in our study, a case control or cohort study must be designed to complete our findings. 5-Critical care medicine has come a long way in the last 20 years. We believe that the quality of care provided in ICUs worldwide has improved, and we are providing compassionate care with augmented monitoring capabilities. However, we still have ways to

go, regarding the prevention and treatment of serious infections that lead to sepsis and septic shock.

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**Conclusion**

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