

# Is hypertriglyceridemia a prognostic factor in sepsis?

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**Introduction:** Sepsis and septic shock are important causes of mortality in intensive care unit patients, hence early diagnosis and therapy are important in management of their treatment. The available information on sepsis patients is not enough to recommend or to discard the routine evaluation of triglyceride (TG) levels at the onset of sepsis. The aim of this study was to investigate the association of hypertriglyceridemia and clinical outcome (or mortality) in patients with severe sepsis.

**Materials and methods:** Between January 1 and December 31, 2011, a total of 84 patients with sepsis from the intensive internal care unit at the Kayseri Training and Research Hospital, Kayseri, Turkey, were investigated retrospectively. Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine/European Society of Intensive Care Medicine consensus conference definitions. For each patient, survival was recorded at the end of the last day of hospitalization as dead or alive. The TG values were taken retrospectively from the records, which were performed routinely for each patient with sepsis at the time of diagnosis. TG >150 mg/dL was considered as hypertriglyceridemia.

**Results:** The percentages of male and female patients were 44% and 56%, respectively. The mean age of patients was 71.49±11.071 years. The percentage of patients with TG values more than 150 mg/dL was 81% (25/31) in the non-survivor group and 19% (6/31) in the survivor group. There was a significant difference regarding TG values between groups ( $P=0.039$ ).

**Discussion:** It was observed in this study that patients in the intensive care unit with sepsis had high TG levels. We also observed that the TG level >150 mg/dL at 0 hour (onset of sepsis) was a significant predictive marker of sepsis mortality rate. The contribution of hypertriglyceridemia to mortality might be modest compared to increase in severity of illness, but, nevertheless, these simple measurements represent a potential therapeutic target in sepsis.

**Keywords:** triglyceride, prognosis, mortality, sepsis

## Introduction

Sepsis and septic shock are important causes of mortality<sup>1</sup> in intensive care unit patients, hence early diagnosis and therapy are important in management of their treatment. Sepsis is defined as the association of a number of nonspecific inflammatory responses with evidence, or suspicion, of a microbial origin.<sup>2,3</sup> The signs and symptoms of sepsis are highly variable. Symptoms are nonspecific but present a picture of systemic illness. Lipopolysaccharide, which is released from the outer membrane of Gram-negative bacteria, plays a key role in initiating the inflammatory response in sepsis. Hypertriglyceridemia is commonly observed in patients with Gram-negative infections and animals administered live Gram-negative bacteria or endotoxin.<sup>4</sup> In one study, the elevation in plasma triglyceride (TG) level observed 24 hours after *Escherichia coli*

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infusion was attributed to a reduction in TG clearance rates rather than an increase in liver secretion.<sup>5</sup> Increased plasma TG concentrations can result from an increased rate of very-low-density lipoprotein (VLDL) secretion from the liver, from a decreased rate of removal of VLDL and TG, or from a combination of changes in both processes. Many of the sepsis-induced disturbances in lipid metabolism are thought to be cytokine related. Tumor necrosis factor (TNF)- $\alpha$  has been shown to elevate serum TG level by increasing the hepatic production<sup>6,7</sup> and also decreasing lipoprotein lipase (LPL) activity in adipose tissue.<sup>8,9</sup> The available information on sepsis patients is not enough to recommend or to discard the routine evaluation of TG levels at the onset of sepsis. The aim of this study was to investigate the association of hypertriglyceridemia and clinical outcome (or mortality) in patients with severe sepsis.

## Materials and methods

Between January 1 and December 31, 2011, a total of 84 patients with sepsis from the intensive internal care unit at the Kayseri Training and Research Hospital, Kayseri, Turkey, were investigated retrospectively, using hospital records. Medical history was recorded from each patient's chart, including age, sex, and chronic background illnesses (ischemic heart disease, diabetes mellitus, hypertension, malignancy, renal failure). Blood pressure, heart rate, and body temperature were recorded for each patient. Laboratory data included: complete blood count; urea; creatinine; glucose; calcium; sodium; potassium; phosphate; uric acid; liver function tests; albumin; and a lipid profile (total cholesterol, calculated serum high-density lipoprotein cholesterol, and TG). Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine/European Society of Intensive Care Medicine consensus conference definitions. The patients included in this study were on broad-spectrum antibiotics and were not taking lipid-lowering drugs. Patients who received enteral or parenteral nutrition within 8 hours before the diagnosis of sepsis were excluded. Those with a history of chronic renal failure, diabetes mellitus, ischemic heart disease, hypertension, or hyperlipidemia were excluded. For each patient, survival was recorded at the end of the last day of hospitalization as dead or alive. The TG values were taken retrospectively from the records, which were performed routinely for each patient with sepsis at the time of diagnosis. At our institution's laboratory, the upper limit for serum TG value is 149 mg/dL. In general, serum TG concentration levels less than 150 mg/dL (less than 1.7 mmol/L) are accepted as normal; 150 to 199 mg/dL (1.7 to 2.2 mmol/L) as close

to high; 200 to 499 mg/dL (2.3 to 5.6 mmol/L) as high; and greater than 500 mg/dL (5.7 mmol/L) as very high.<sup>10</sup> Thus, before data analysis, hypertriglyceridemia was defined as any TG level  $\geq 150$  mg/dL.

## Statistical analysis

For statistical analysis, the Statistical Package for the Social Sciences ([SPSS] v 16; IBM Corporation, Armonk, NY, USA) was used. Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. We reported continuous data as mean and standard deviation. Categorical variables were summarized as percentages and compared with the chi-square test. The chi-square test was used to evaluate the relationship between TG levels and mortality.  $P$ -values  $< 0.05$  were considered significant. To evaluate the relationship between biochemical parameters and mortality, independent samples  $t$ -test was used. In addition, mean and frequency analysis were used.

## Results

The percentages of male and female patients were 44% and 56%, respectively. The mean age of patients was  $71.49 \pm 11.071$  years. Considering the patients as survivors or non-survivors, the mean age of patients was  $68.19 \pm 13.88$  years in the survivor group and  $72.97 \pm 9.31$  years in the non-survivor group ( $P=0.019$ ). When biochemical parameters were evaluated, no significant difference was found between survivor and non-survivor groups. The mean TG level of patients was  $122.96 \pm 65.01$  mg/dL in the survivor group and  $167.42 \pm 109.58$  mg/dL in the non-survivor group ( $P=0.083$ ). The relationship of biochemical parameters and mortality in patients with sepsis is given in Table 1. TG  $> 150$  mg/dL was considered as hypertriglyceridemia. The percentage of patients with TG values more than 150 mg/dL was 81% (25/31) in the non-survivor group and 19% (6/31) in the survivor group. For the TG values, there was a significant difference between the two groups ( $P=0.039$ ). Values for each group are given in Table 2. The risk of mortality in the group of patients with high TG levels was 81%, compared to 58% in the group with normal TG levels. The odds for mortality were 4.1 (25/6) and 1.4 (28/20), respectively. We calculated and added the risk ratio ( $0.806/0.583=1.382$ ) and the odds ratio ( $4.1/1.4=2.928$ ).

## Discussion

In this study, it was observed that patients in the intensive care unit with sepsis had high TG levels. Lipoproteins have been known to play a role in innate immunity and variations

**Table 1** The relationships between biochemical parameters and mortality in patients with sepsis

Parameter	N	Mean $\pm$ standard deviation	P-value
Age, years			0.019
Non-survivor	58	72.97 $\pm$ 9.31	
Survivor	26	68.19 $\pm$ 13.88	
Glucose, mg/dL			0.483
Non-survivor	58	147.78 $\pm$ 99.78	
Survivor	26	145.58 $\pm$ 89.12	
Blood urea nitrogen, mg/dL			0.709
Non-survivor	58	65.87 $\pm$ 36.51	
Survivor	26	48.58 $\pm$ 37.69	
Creatine, mg/dL			0.765
Non-survivor	58	3.40 $\pm$ 2.35	
Survivor	26	2.11 $\pm$ 2.59	
Aspartate, IU/L			0.054
Non-survivor	58	96.91 $\pm$ 221.27	
Survivor	25	47.80 $\pm$ 49.05	
Aspartate, IU/L			0.302
Non-survivor	58	67.69 $\pm$ 169.81	
Survivor	25	47.08 $\pm$ 77.07	
Alkaline phosphatase, IU/L			0.071
Non-survivor	52	115.88 $\pm$ 73.58	
Survivor	25	141.44 $\pm$ 101.21	
Sodium, mmol/L			0.288
Non-survivor	58	140.34 $\pm$ 11.60	
Survivor	25	138.00 $\pm$ 7.46	
Potassium, mmol/L			0.391
Non-survivor	57	4.46 $\pm$ 0.86	
Survivor	24	4.49 $\pm$ 1.30	
Triglycerides, mg/dL			0.083
Non-survivor	53	167.42 $\pm$ 109.58	
Survivor	26	122.96 $\pm$ 65.01	

in their levels have been observed in a variety of inflammatory disorders, but not much is known about lipoprotein metabolism in patients with sepsis. Elevated plasma TG level may result either from a decreased rate of peripheral removal or an increased rate of production and secretion of liver. Previous data, showing a reduction in LPL activity in peripheral tissues of Gram-negative septic rats<sup>11–13</sup> and septic patients,<sup>14</sup> suggest a defect in the clearance of TG as one of the factors involved in the cause of hypertriglyceridemia. The observed decrease in tissue LPL activity in rats administered live *E. coli* was also expected, since postheparin plasma lipase

**Table 2** The relationship between triglyceride levels and mortality in patients with sepsis

Triglyceride level, mg/dL	Non-survivor, n (%)	Survivor, n (%)	P-value
Triglycerides > 150	25 (81)	6 (19)	0.039
Triglycerides < 150	28 (58)	20 (42)	

activity and adipose tissue LPL activity have been reported to be decreased in bacteremic monkeys and rats, respectively.<sup>15,16</sup> Concomitant with the reduced enzyme activities, circulating TG concentrations were increased. The initial rise in serum TG level in the *E. coli*-treated rats may have been mediated by the increased concentrations of plasma catecholamines and glucocorticoids, which are also elevated in rat models of endotoxemia,<sup>17,18</sup> polymicrobial sepsis,<sup>19</sup> and *E. coli* bacteremia.<sup>20</sup> Recently, catecholamines have been shown to mediate endotoxin-induced hypertriglyceridemia, may contribute to the downregulation of adipose LPL.<sup>21</sup> Epinephrine has also been shown to lower LPL activity in adipocytes by way of decreasing LPL synthesis.<sup>22</sup> Cytokines such as TNF- $\alpha$  and the interleukins may mediate the hypertriglyceridemia associated with sepsis and endotoxemia.<sup>23</sup> A study on endotoxin-injected rats with suppressed LPL tissue activities showed that the hypertriglyceridemia was the result of a reduction in the clearance rate of TG from the plasma.<sup>24</sup> Endotoxemia<sup>25</sup> and polymicrobial sepsis<sup>26</sup> have also been shown to have produced an elevation in serum TNF- $\alpha$  at the 60th minute. TNF administration was shown to produce a rapid rise in serum TG level between the 45th and 90th minutes, which was due to an increase in hepatic TG synthesis and VLDL secretion.<sup>27,28</sup> Other cytokines, such as interferons, the interleukins, and platelet-activating factor, may also have a role in altering lipid metabolism after *E. coli* sepsis.<sup>29,30</sup> One study showed that the hypertriglyceridemia of sepsis may have a protective function.<sup>31</sup> Lipoproteins bind endotoxin, thus preventing their interaction with lipopolysaccharide-binding protein and, subsequently, their uptake by macrophages that triggers the release of the inflammatory mediators.<sup>31</sup> We have also observed that the TG level >150 mg/dL at 0 hour (onset of sepsis) was a significant predictive marker of sepsis mortality rate, and hypertriglyceridemia can be defined as a risk factor for mortality in patients with sepsis.

The contribution of hypertriglyceridemia to mortality might be modest compared to increase in severity of illness, but, nevertheless, these simple measurements represent a potential therapeutic target in sepsis. The mechanism that modifies TG level in sepsis is not yet well understood, and further studies in larger populations with sequential cholesterol monitoring for a longer period will lead to more timely interventions and enhance patient outcomes.

## Conclusion

According to our results, the routine measurement of serum TGs at the onset of sepsis and sequential monitoring are recommended. The measurement of TG can be a good

predictor of hospital death in sepsis ; however, from the observations of the present study, we suggest that new therapies directed at decreasing serum TG levels may offer important alternative options for better management of sepsis.

## Disclosure

The authors have no conflicts of interest to report in this work.

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