Serum Cholesterol and Mortality in Patients with Multiple Organ Failure

To the Editor:

Multiple organ failure is a major cause of death in hospitalized patients in the intensive care unit (1). Despite modern treatment strategies, no decrease of mortality during the last decades can be noted. The standard clinical and laboratory diagnostic variable, although specific, may not always reflect metabolic dysfunction, severity of disease, and risk of death in critically ill patients. In 1911, Chauffard et al. (2) reported a decrease in serum cholesterol levels in febrile patients. Since then, a number of studies have described hypocholesterolemia in association with mortality in inflammation (3). However, no information is available concerning a critical threshold concentration of cholesterol during severe inflammation.

In the present study, plasma levels of cholesterol, triglycerides, apolipoprotein (apo)A1, apoB, lipoprotein(a), tumor necrosis factor (TNF), soluble TNF receptors, and interleukin-6 were measured in a cohort of 33 critically ill patients with multiple organ failure (Acute Physiology and Chronic Health Evaluation [APACHE] II score 32 ± 6; range, 20–44). Patients were consecutively included in the study when APACHE score was >20. Underlying diseases were as follows: cancer (1 testicular cancer, 2 non-Hodgkin's lymphoma, 2 myelodysplastic syndrome, 1 esophageal cancer, 1 metastatic mammary cancer, 1 metastatic prostate cancer, 1 plasmocytoma, 1 renal cell cancer, 1 acute myeloic leukemia), 16 with coronary heart disease, of these, seven with myocardial infarction, 1 Wegener's granulomatosis, 3 diabetes mellitus (including 1 diabetic coma), 1 chronic alcoholism, and 1 pneumonia without underlying disease. In total, 52% of the patients (Elebute score, >12; n = 11) (4) were septic, and 11 patients fulfilled the criteria of septic shock (mean arterial blood pressure <60 mm Hg; heart rate 123 ± 31 beats/min). In all patients on the day of study inclusion, we measured very low plasma cholesterol concentration of 83 ± 30 mg/dL (range, 41–158 mg/dL) in comparison to healthy volunteers, who had a mean plasma cholesterol of 180 ± 22 mg/dL (range, 149–231 mg/dL; n = 10). Survivors (28-day mortality) had significantly higher plasma cholesterol (100 ± 33 mg/dL; range, 50–158 mg/dL) as compared to nonsurvivors (73 ± 24 mg/dL, 41–127 mg/dL; $p < .05$). Circulating triglyceride levels, as well as apoA-1 and lipoprotein(a) levels, did not significantly differ between survivors and nonsurvivors. However apoB levels were significantly lower in nonsurvivors compared with survivors (61.6 ± 21.8 mg/dL vs. 76.0 ± 23.9 mg/dL; $p < .05$).

All three patients with very low plasma cholesterol (<50 mg/dL) were nonsurvivors, whereas only 1 of 5 patients with cholesterol >120 mg/dL died (Fig. 1). Patients with plasma cholesterol between 50 mg/dL and 80 mg/dL had a mortality rate of 73% while those with plasma cholesterol between 81 mg/dL and 120 mg/dL had a mortality of 50%. No correlation between cholesterol and APACHE II score was evident, but severity of disease based on Elebute score (4) correlated inversely with cholesterol ($r^2 = 0.15$; $p < .05$). Although the mechanism underlying cholesterol decrease during inflammation is still unknown, cytokine release (which is an essential early immune response to inflammation) may be one important factor leading to the reduction in circulating cholesterol. *In vitro* studies as well as reports in experimental animals suggest that lipoproteins have a protective effect in endotoxemia possibly as a result of binding and neutralization of endotoxin (5). In our study, decrease in plasma cholesterol was accompanied by increase in circulating plasma TNF levels that was not statistically significant. However, soluble TNF receptors, which

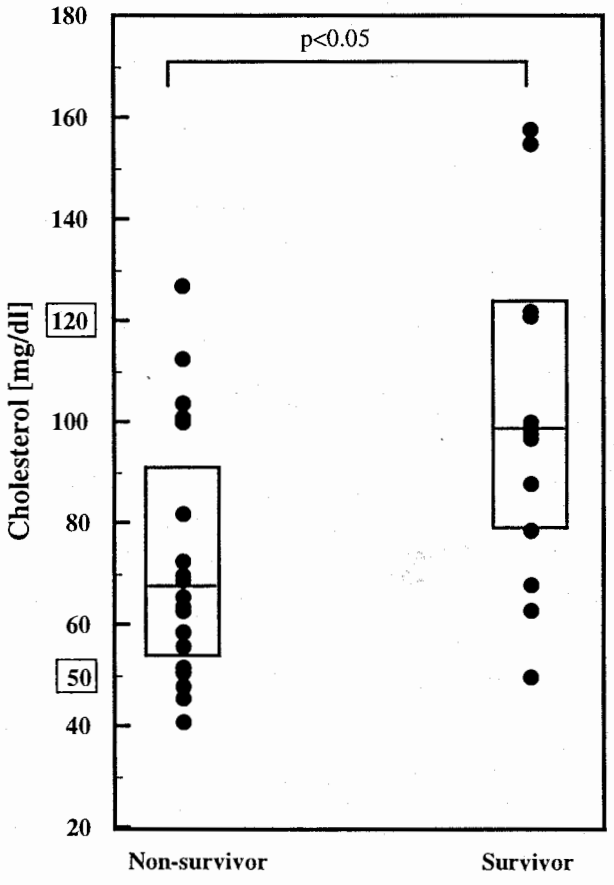

Figure 1. Cholesterol serum levels in survivors and nonsurvivors. *Boxes* represent the two middle quartiles divided by the *median point*.

Address requests for reprints to: Peter Fraunberger, MD, Institute of Clinical Chemistry, Klinikum Grosshadern, 81366 Munich, Germany.

Table 1. Clinical scores and plasma levels of interleukin (IL)-6, tumor necrosis factor (TNF), and its soluble receptors in patients with multiple organ failure in relation to survival

	Nonsurvivor (n = 20)	Survivor (n = 13)
APACHE II score	32 (26–44)	29 (20–43)
Elebute score	14 (8–22)	11 (1–21)[a]
Cholesterol (mg/dL)	73 (41–127)	100 (50–158)[a]
Triglycerides (mg/dL)	113 (64–225)	122 (55–286)
IL-6 (pg/mL)	731 (27–14000)	249 (96–1261)[a]
TNF (pg/mL)	49 (20–358)	35 (15–69)
TNFR p55 (ng/mL)	10.8 (2.7–50.0)	5.4 (3.1–29.8)[a]
TNFR p75 (ng/mL)	15.6 (5.3–37)	7.3 (3.3–25.2)[a]

APACHE, Acute Physiology and Chronic Health Evaluation; TNFR, tumor necrosis factor receptor.
[a] $p < .05$ (statistically significant. Values expressed as mean (range).

are shed in response to TNF release have a higher biological half-life than free TNF, and their circulating levels correlated inversely with plasma cholesterol (TNF receptor p55: $r^2 = 0.13$, TNF receptor p75: $r^2 = 0.12$; $p < .05$) (Table 1).

Serum cholesterol levels are not affected by diet or drug therapy employed in septic patients. They may therefore reflect a metabolic response of the organism to the inflammatory condition. Changes in total cholesterol and lipoprotein pattern and profile has been found during various inflammatory diseases such as burn injuries, which lead to a profound decrease of cholesterol within a few days (6). Both low density lipoprotein and high density lipoprotein, which carry >80% of total cholesterol in humans decreased. In contrast, triglyceride-rich very low density lipoprotein increased in the acute phase. Similarly, in patients with sepsis, a decrease in serum levels of total cholesterol, high density lipoprotein cholesterol and apoA-1 and apoB and an increase of serum triglycerides have also been reported (7). These changes in lipoprotein profile were independent of the underlying disease or infectious agents causing sepsis. Sammalkorpi et al. (8) confirmed these results in patients with bacterial and viral infections. In addition, some recent studies reported very low levels of total cholesterol levels in critically ill patients (9), trauma patients (10), and in patients after major surgery postoperatively (11). The degree of hypocholesterolemia in all these studies seem to depend on the severity of the disease, with the lowest levels in critically ill patients with sepsis. This is supported by the observation that in our patients an inverse correlation existed between Elebute score as a marker for severity of disease as well as between mortality and cholesterol levels. Studies with a higher number of patients are necessary to establish that circulating cholesterol is an independent marker for severity of disease in critically ill patients.

Peter Fraunberger, MD, Dorothea Nagel, PhD, Autar K. Walli, PhD, Dietrich Seidel, MD, Institute of Clinical Chemistry, Klinikum Großhadern, University Munich, Munich, Germany; Karl Werdan, MD, Department of Medicine III, Klinikum Kröllwitz, University Halle-Wittenberg, Halle, Germany

REFERENCES

1. Deitch EA: Multiple organ failure. Pathophysiology and potential future therapy. *Ann Surg* 1992; 216:117–134
2. Chauffard A, Richet C, Grigaut A: La cholesterinemia au cours de la tuberculose pulmonaire. *Compt Rend Soc Biol* 1911; lxx: 276–277
3. Windler E, Ewers-Grabow U, Thiery J, et al: The prognostic value of hypocholesterolemia in hospitalized patients. *Clin Invest* 1994; 72:939–943
4. Elebute EA; Stone HB: The grading of sepsis. *Br J Surg* 1983; 70:29–31
5. Feingold KR, Funk JL, Moser AH, et al: Role for circulating lipoproteins in protection from endotoxin toxicity. *Infect Immun* 1995; 63:2041–2046
6. Coombes EJ, Shakespeare PG, Batstone GF: Lipoprotein changes after burn injury in man. *J Trauma* 1980; 20:971–975
7. Alvarez C, Ramos A: Lipids, lipoproteins, and apoproteins in serum during infection. *Clin Chem* 1986; 32:142–145
8. Sammalkorpi K, Valtonen V, Kertulla Y, et al: Changes in serum lipoprotein pattern induced by acute infections. *Metabolism* 1988; 37:859–865
9. Gordon BR, Parker TS, Levine DM, et al: Low lipid concentration in critical illness: Implications for preventing and treating endotoxemia. *Crit Care Med* 1996; 24:584–589
10. Elliot DC, Wiles CE: Low lipid concentrations in critical illness: Hypocholesterolemia among trauma patients. *Crit Care Med* 1997; 25:1437–1439
11. Akgün S, Ertel NH, Mosenthal A, et al: Postsurgical reduction of serum lipoproteins: Interleukin-6 and the acute phase response. *J Lab Clin Med* 1998; 131:103–108