

## Commentary

**Hypocholesterolemia in sepsis and critically ill or injured patients**Robert F Wilson<sup>1</sup>, Jeffrey F Barletta<sup>2</sup> and James G Tyburski<sup>3</sup><sup>1</sup>Professor of Surgery, Department of Surgery, Wayne State University School of Medicine, Detroit Receiving Hospital, Detroit, Michigan, USA<sup>2</sup>Department of Pharmacology, Wayne State University School of Medicine, Detroit Receiving Hospital, Detroit, Michigan, USA<sup>3</sup>Associate Professor of Surgery, Department of Surgery, Wayne State University School of Medicine, Detroit Receiving Hospital, Detroit, Michigan, USA

Correspondence: Robert F Wilson

Published online: 6 October 2002

*Critical Care* 2003, **7**:413-414 (DOI 10.1186/cc2390)This article is online at <http://ccforum.com/content/7/6/413>

© 2003 BioMed Central Ltd (Print ISSN 1364-8535; Online ISSN 1466-609X)

**Abstract**

Hypocholesterolemia is an important observation following trauma. In a study of critically ill trauma patients, mean cholesterol levels were significantly lower ( $119 \pm 44$  mg/dl) than expected values ( $201 \pm 17$  mg/dl). In patients who died, final cholesterol levels fell by 33% versus a 28% increase in survivors. Cholesterol levels were also adversely affected by infection or organ system dysfunction. Other studies have illustrated the clinical significance of hypocholesterolemia. Because lipoproteins can bind and neutralize lipopolysaccharide, hypocholesterolemia can negatively impact outcome. New therapies directed at increasing low cholesterol levels may become important options for the treatment of sepsis.

**Keywords** endotoxemia, hypocholesterolemia, hypolipidemia, outcome, trauma

It was a pleasure to read the report from Dunham and coworkers [1] concerning the relationship between hypocholesterolemia and outcome in patients following severe trauma. Although their study involved only 28 patients, these patients were severely injured (Injury Severity Score  $31 \pm 9$ ) and they required at least 7 days of mechanical ventilation. Upon admission to the surgical intensive care unit the mean cholesterol level was only  $119 \pm 44$  mg/dl, as compared with the expected normal cholesterol level (taken from a database) of  $201 \pm 17$  mg/dl ( $P < 0.001$ ). In the patients who died ( $n = 3$ ), the final cholesterol values were 33% lower than their initial postinjury levels, whereas in patients who survived the final cholesterol levels had risen by 28%. Interestingly, the initial postinjury levels were considerably higher in the three patients who died than in those who survived ( $175 \pm 62$  mg/dl versus  $112 \pm 37$  mg/dl).

Although these results are impressive, it is unknown whether the expected (preadmission) cholesterol values used as control, which were acquired from the general population, are consistent with those observed in the trauma population. It would have been interesting to know the actual preadmission cholesterol levels (obtained either retrospectively or through

follow-up evaluation); complete lipid profiles (e.g. triglycerides, very-low-density lipoprotein, low-density lipoprotein [LDL], high-density lipoprotein [HDL]), including how each was individually affected; cytokine data (especially tumor necrosis factor- $\alpha$ , IL-6) to correlate with cholesterol levels; and nutritional status (especially lipid intake) of these patients.

Dunham and coworkers also noted a relationship between cholesterol levels and infection. Cholesterol levels either remained low or fell in 90% of patients presenting with an infection. This response was more often associated with infection than with traditional markers such as leukocyte response, which was positive in only 61% of patients. Cholesterol levels also decreased with the onset of each organ system dysfunction (ratio of arterial oxygen tension to fractional inspired oxygen  $< 350$ , creatinine  $> 2.0$  mg/dl, glucose  $> 120$  mg/dl, bilirubin  $> 2.5$  mg/dl, arterial bicarbonate  $\geq 28$  or  $\leq 23$  mmol/l;  $P < 0.01$ ).

The findings of Dunham supplement the literature concerning hypocholesterolemia and critical illness [2].

Hypocholesterolemia was first reported in 1911, when Chauffard and coworkers reported decreased cholesterol

levels in patients who were in 'very bad general condition' during the febrile phase of tuberculosis. In 1920, Kipp noted a relationship between the degree of hypocholesterolemia and the severity of infection. We were unable to identify other articles about hypocholesterolemia following injury or infection in the literature until 1980, when an article by Coombes and coworkers [3] was published that described the changes in lipoproteins after burn injury. Those investigators observed a profound decrease in cholesterol levels within a few days of the burn, with the lowest values occurring between the days 6 and 10. They noted that both LDL and HDL, which carry over 80% of the total cholesterol in humans, were both decreased. In contrast, triglyceride-rich very-low-density lipoproteins increased in the acute phase.

Of the various reasons offered for the hypocholesterolemia seen in critically ill and injured patients, especially those with sepsis, one that seems especially important is related to the ability of lipids and lipoproteins to bind to and neutralize bacterial endotoxin (lipopolysaccharide [LPS]) [4]. It has been noted that LPS in blood binds to LPS binding protein [5], activating the cell surface CD14 receptor [6]. This stimulates the release of a cascade of proinflammatory cytokines, including tumor necrosis factor- $\alpha$ , IL-1, and IL-6 [7]. If LPS binds to lipoproteins (e.g. cholesterol), then cytokine release is decreased [8].

Animal experiments appear to corroborate this interaction. For example, transgenic mice with elevated HDL [9] or LDL concentrations [10] are protected against lethal endotoxemia and severe Gram-negative infections. Indeed, infusion of HDL blocked LPS-induced cytokine production in rabbits [11] and protected against lethal doses of endotoxin in mice [9]. The administration of HDL to human volunteers also blocks many of the effects seen with infusion of LPS [12,13].

Clinical support was provided by Gordon and coworkers [14], who recently (2001) reported low cholesterol and lipoprotein concentrations in 111 critically ill surgical patients. They noted that these levels correlated inversely with concentrations of IL-6, soluble IL-2 receptor, and IL-10. The lowest cholesterol and lipoprotein levels also predicted a poor clinical outcome. Those investigators suggested that hypolipidemia (hypocholesterolemia) is an independent predictor of clinical outcome in critically ill patients. They also implied that a vicious cycle is initiated in many critically ill patients with acute sepsis with an increased production of inflammatory cytokines, which then decreases lipid and lipoprotein concentrations and increases the susceptibility to LPS.

Dunham and coworkers should be congratulated for their contribution to this growing body of evidence and its implications for future treatments. If there were a way to increase the low lipid concentrations in these patients, then this could be an important therapeutic option for preventing and treating sepsis.

## Competing interests

None declared.

## References

- Dunham CM, Fealk MH, Sever WE: **Following severe injury, hypocholesterolemia improves with convalescence but persists with organ failure or onset of infection.** *Crit Care* 2003, **7**: R145-R153.
- Fraunberger P, Schaefer S, Werdan K, Walli AK, Seidel D: **Reduction of circulating cholesterol and apolipoprotein levels during sepsis.** *Clin Chem Lab Med* 1999, **37**:357-362.
- Coombes EJ, Shakespeare PG, Batstone GF: **Lipoprotein changes after burn injury in man.** *J Trauma* 1980, **20**:971-975.
- Harris HW, Grunfeld C, Feingold KR, Read TE, Kane JP, Jones AL, Eichbaum EB, Bland GF, Rapp JH: **Chylomicrons alter the fate of endotoxin, decreasing tumor necrosis factor release and preventing death.** *J Clin Invest* 1993, **91**:1028-1034.
- Tobias PS, Soldau K, Ulevitch RJ: **Identification of a lipid A binding site in the acute phase reactant lipopolysaccharide binding protein.** *J Biol Chem* 1989, **264**:10867-10871.
- Wright SD, Ramos RA, Tobias PS, Ulevitch RJ, Mathison JC: **CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein.** *Science* 1990, **249**:1431-1433.
- Schumann RR, Leong SR, Flaggs GW, Gray PW, Wright SD, Mathison JC, Tobias PS, Ulevitch RJ: **Structure and function of lipopolysaccharide binding protein.** *Science* 1990, **249**:1429-1431.
- Baumberger C, Ulevitch RJ, Dayer JM: **Modulation of endotoxic activity of lipopolysaccharide by high-density lipoprotein.** *Pathobiology* 1991, **59**:378-383.
- Levine DM, Parker TS, Donnelly TM, Walsh A, Rubin AL: **In vivo protection against endotoxin by plasma high density lipoprotein.** *Proc Natl Acad Sci USA* 1993, **90**:12040-12044.
- Netea MG, Demacker PN, Kullberg BJ, Boerman OC, Verschuuren I, Stalenhoef AF, van der Meer JW: **Low-density lipoprotein receptor-deficient mice are protected against lethal endotoxemia and severe Gram-negative infections.** *J Clin Invest* 1996, **97**:1366-1372.
- Hubsch AP, Powell FS, Lerch PG, Doran JE: **A reconstituted, apolipoprotein A-I containing lipoprotein reduces tumor necrosis factor release and attenuates shock in endotoxemic rabbits.** *Circ Shock* 1993, **4**:14-23.
- Pajkrt D, Lerch PG, van der Poll T, Levi M, Illi M, Doran JE, Arnet B, van den Ende A, ten Cate JW, van Deventer SJ: **Differential effects of reconstituted high-density lipoprotein on coagulation, fibrinolysis and platelet activation during human endotoxemia.** *Thromb Haemost* 1997, **77**:303-307.
- Gordon BR, Parker TS, Levine DM, Saal SD, Wange JCL, Sloan BJ, Barie PS, Rubin AL: **Low lipid concentrations in critical illness: Implications for preventing and treating endotoxemia.** *Crit Care Med* 1996, **24**:584-589.
- Gordon BR, Parker TS, Levine DM, Saal SD, Wange JCL, Sloan BJ, Barie PS, Rubin AL: **Relationship of hypolipidemia to cytokine concentrations and outcomes in critically ill surgical patients.** *Crit Care Med* 2001, **29**:1563-1568.