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Inflammation, cholesterol levels, and risk of mortality among patients receiving dialysis.

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population are due to the cholesterol-lowering effect of malnutrition and systemic inflammation, rather than to a protective effect of high cholesterol levels. However, there is considerable epidemiologic, clinical, and laboratory evidence that high cholesterol levels protect against infections, while low cholesterol levels predispose to infections.[2]

For instance, in a 15-year follow-up study of more than 100 000 healthy individuals, cholesterol levels were inversely associated with the risk of being admitted to the hospital with a diagnosis of infectious disease.[3] Evidently, low cholesterol levels analyzed at baseline could not have been caused by a disease these individuals had not yet acquired. Children with Smith-Lemli-Opitz syndrome have extremely low cholesterol levels and experience frequent and severe infections, which can be prevented with supplementary dietary cholesterol.[4]

Numerous experimental studies have demonstrated an important role of low-density lipoprotein cholesterol (LDL-C) as an effective inhibitor of bacterial toxins. For instance, the survival of rats with experimental hypolipidemia challenged with lipopolysaccharide or gram-negative bacteria is much lower, and the survival of mice with familial hypercholesterolemia challenged similarly is much higher than normal.[5]

Finally, in at least 7 studies of people aged 60 and older, total mortality was inversely associated with cholesterol levels, or high cholesterol levels were associated with longevity.[2]

Therefore, if statin treatment should be used in dialysis patients, it may be wise to use the lowest possible dose, if any at all.

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1. Liu Y, Coresh J, Eustace JA, et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA*. 2004; 291:451-459.
2. Ravnskov U. High cholesterol may protect against infections and atherosclerosis. *QJM*. 2003;96:927-934.
3. Iribarren C, Jacobs DR Jr, Sidney S, Claxton AJ, Feingold KR. Cohort study of serum total cholesterol and in-hospital incidence of infectious diseases. *Epidemiol Infect*. 1998;121:335-347.
4. Elias ER, Irons MB, Hurley AD, Tint GS, Salen G. Clinical effects of cholesterol supplementation in six patients with the Smith-Lemli-Opitz syndrome (SLOS). *Am J Med Genet*. 1997;68:305-310.
5. Feingold KR, Funk JL, Moser AH, Shigenaga JK, Rapp JH, Grunfeld C. Role for circulating lipoproteins in protection from endotoxin toxicity. *Infect Immun*. 1995; 63:2041-2046.

To the Editor: We are concerned that the sample of Dr Liu and colleagues[1] may not be representative of US patients who receive dialysis. The median age of patients receiving incident dialysis in the United States is 64.5 years,[2] whereas in the study by Liu et al it was 57.2 years for all patients and 53.7 years for those without malnutrition-inflammation complex syndrome (MICS). The renal transplant rate in the US dialysis population is approximately 5.5 per 100 patient-years.[2] One would thus expect 103 in the cohort of Liu et al, but this is substantially fewer than the 153 the authors reported. Hence, the younger age and the higher transplant rate in this study indicate a dialysis population that is substantially healthier than average.

The authors stated that their findings support aggressive treatment of hypercholesterolemia in patients receiving dialysis. We disagree with this conclusion, as the authors' own analyses in the subgroup of patients with MICS, who comprise 75% of all patients of the study, indicate either inverse or no association between total serum cholesterol levels and outcome, even after adjustments for MICS. These findings indicate a strong association between elements of malnutrition-inflammation and prospective mortality in patients undergoing dialysis. Hence, the treatment of MICS may have a higher priority than treatment of hypercholesterolemia or other conventional cardiovascular risk factors in patients receiving dialysis.[3]

Moreover, it is possible that decreasing serum cholesterol levels in these patients is harmful, since the lipoprotein pool may serve as an effective scavenger to bind with and neutralize the circulating lipopolysaccharides (ie, bacterial endotoxin) in patients with heart failure and fluid overload,[4] a common condition in patients receiving dialysis. Low levels of serum lipoproteins, including cholesterol, may be associated with increased levels of unbound circulating lipopolysaccharides and a higher prevalence of inflammation and cachexia.[4,5] To our knowledge, there are few published studies suggesting that high cholesterol levels and obesity are related to impaired survival among patients with chronic illness. Therefore we caution against the authors' use of the term "spurious" for the paradoxically inverse associations that have been consistently observed between such conventional risk factors as hypercholesterolemia and obesity and improved survival in patients receiving maintenance dialysis.

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1. Liu Y, Coresh J, Eustace JA, et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA*. 2004; 291:451-459.
2. US Department of Public Health and Human Services. United States Renal Data System. 2003. Available at: http://www.usrds.org. Accessed March 25, 2004.
3. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int*. 2003; 63:793-808.
4. Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. *Lancet*. 2000;356:930-933.
5. Niebauer J, Volk HD, Kemp M, et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. *Lancet*. 1999;353:1838-1842.

In Reply: Dr Ravnskov and Drs Kalantar-Zadeh and Anker argue that high cholesterol levels may confer protection against infection and circulating lipopolysaccharides (ie, bacterial endotoxin) and that hypercholesterolemia should not be treated among patients receiving dialysis. Ravnskov cites the protective effects of dietary cholesterol supplementation in children with Smith-Lemli-Opitz syndrome, in whom cholesterol levels are extremely low (approximately 8-62 mg/dL [0.21-1.61 mmol/L]), as well as epidemiologic findings that low total cho-