

see original article on page 1063

C-reactive protein and dialysis access

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Hemodialysis patients have greater morbidity and mortality when they have a catheter rather than an arteriovenous fistula access. Catheter infection plays a significant role in this effect. Inflammation associated with dialysis catheter use could have an independent adverse effect on patient outcomes. Awareness and further study of the role of inflammation are needed.

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Use of a dialysis catheter rather than an arteriovenous fistula is associated with higher dialysis patient mortality. Higher rates of infection account for part of this effect. Inflammation could play an additional role.

Goldstein *et al.*¹ (this issue) report that a change of dialysis access from a catheter to a fistula is accompanied by a significant fall in the serum level of C-reactive protein (CRP), and reduction of inflammation. These findings were in patients who did not have evident catheter infections. This should provide yet further impetus to use fistulas rather than catheters in our hemodialysis patients.

Some issues remain, however. The first is that in this report, information on long-term outcome is not provided, either for morbidity and mortality or for quality of life. One can assume that a fall in the CRP level is a good thing, and that such a drop may reduce cardiovascular morbidity and mortality, but assumption is not fact. A second point is that other markers of inflammation, such as the white blood cell count, were not reported, even though the latter is a long-established correlate of

cardiovascular pathology.² A final concern is that there can be substantial variation in the CRP level in a given patient, and single values of CRP were used by Goldstein *et al.*,¹ rather than multiple ones. Still, the patterns of change in CRP levels are distinct and differ between those who got a fistula and those who remained with a dialysis catheter.

Catheters are to be avoided, then, not just because they are associated with worse outcomes, but now also because they are a proinflammatory stimulus, perhaps contributing by that mechanism to their association with greater mortality. To firm up this mechanistic link, one should ask two questions. First, is inflammation mechanistically important in affecting morbidity and mortality in nonrenal disease? Second, are there experimental data to support this link? There is a known surfeit of cardiovascular mortality in subjects with rheumatoid arthritis, an obvious inflammatory condition.³ Also, a lipopolysaccharide model of chronic inflammation in rats caused them to have cardiac fibrosis and microvascular injury.⁴ But it is not established that this occurs via CRP. The mechanistic role of CRP can be tested by mendelian randomization. This technique identifies subjects with genetically determined differences in a particular trait and tests whether the putative effect of that trait indeed corresponds to the genetically determined differences. For subjects with metabolic syndrome,

genetic variation in CRP did not affect cardiovascular outcomes.⁵

There are further practical limits. First, there probably is a limit to our ability to reduce mortality in subjects with end-stage renal disease. Go *et al.* show clearly the 15% yearly mortality of subjects with chronic renal failure who are not (yet) on dialysis.⁶ It is hard to imagine that we will be able to reduce the yearly mortality of people on dialysis to a lesser percentage than those 15%. Second, although it is a laudable goal to reduce catheter use, clinician nephrologists know that this is often not possible. Vascular arteriovenous access may be impossible, for instance because of bad vascular disease. So, too, may some patients refuse to have an arteriovenous fistula created. They prefer the painless access of a catheter, and they do not make the connection between worse outcomes and catheters, in part because those outcomes occur in the hospital and are not visible to them in the outpatient dialysis unit. In future studies comparing catheters with fistulas, it could be informative to test quality of life, using tools such as the SF-36 health survey.

Nonetheless, it is rational to pay attention to markers of morbidity and future mortality. When the CRP level is above 3 mg/l, a dialysis patient may have an adverse outcome (Figure 1). This may be recognized clinically by a poor appetite, or by the presence of itching.^{7,8} Creating a fistula should avoid the acknowledged adverse effects of a catheter—infection, clotting, underdialysis—and could also reduce the inflammatory CRP. If that switch in access cannot be made, there may be other measures that may reduce the CRP. The recent JUPITER study reported a benefit of rosuvastatin to reduce the low-density lipoprotein cholesterol and the CRP in subjects without kidney disease, but statins have been tested in dialysis patients and do not improve survival.^{9,10} If lowering of the CRP is still wanted, one can consider treatment for periodontal disease, a Mediterranean diet, and the tasty option of eating dark chocolate.^{11–13}

One must also consider whether lowering the blood CRP level is always a good thing, and whether an elevated CRP may have some

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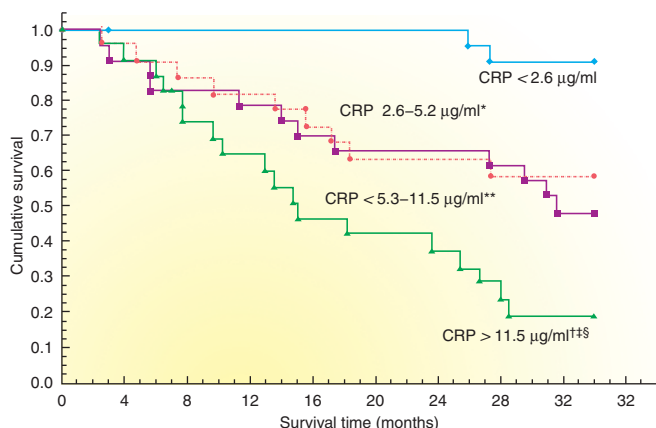


Figure 1 | Kaplan–Meier estimate of survival in hemodialysis patients with serum C-reactive protein (CRP) levels in the highest quartile, middle two quartiles, and lowest quartile.

* $P=0.0015$ vs CRP <2.6 $\mu\text{g/ml}$; ** $P=0.0090$ vs CRP <2.6 $\mu\text{g/ml}$; † $P=0.0028$ vs CRP 2.6 – 5.2 $\mu\text{g/ml}$; ‡ $P=0.0012$ vs CRP <5.3 – 11.5 $\mu\text{g/ml}$; § $P=0.0001$ vs CRP <2.6 $\mu\text{g/ml}$. (Adapted with permission from ref. 15.)

good associated with it. The CRP molecule has existed for hundreds of millions of years. It is a pentamer exported from the liver and is part of our innate immunity. It assists in bacterial killing, for instance, via complement and via opsonization. It may also assist in eliminating apoptotic and necrotic tissue.¹⁴ Long-term studies of CRP need to watch for any adverse effects of hobbling this innate defense.

DISCLOSURE

The authors declared no competing interests.

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