Plasma hepcidin levels are elevated but responsive to erythropoietin therapy in renal disease

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To the Editor: We read with great interest the article by Ashby *et al.*[1] reporting that plasma hepcidin-25 levels—measured by a novel radioimmunoassay—are elevated in renal disease, and that this mechanism is positively correlated with ferritin level but inversely correlated with glomerular filtration rate.

Ashby *et al.* reported, unlike another recent study,[2] that hepcidin-25 levels did not decrease at all in six patients during a single 'standard' hemodialysis (HD) session. This finding is surprising given the molecular weight of hepcidin-25 (2789 Da[2]), thus predicting substantial clearance at least by high-flux HD membranes.[3] In order to understand these discrepancies, could the authors detail what is currently a 'standard' HD procedure in London?

In addition, by multivariate regression analysis, cholesterol level was found to be inversely correlated ($P = 0.018$) with plasma hepcidin level among 94 hemodialyzed patients, which is a finding that was not discussed by the authors. Fluvastatin 80 mg per day was recently shown to decrease not only total cholesterol and high-sensitive C-reactive protein levels, but also prohepcidin serum levels in dyslipidemic dialyzed patients.[4] We therefore wonder whether statin use might account for the negative independent relationship between hepcidin and cholesterol levels in the study of Ashby *et al.*

1. Ashby DR, Gale DP, Busbridge M *et al.* Plasma hepcidin levels are elevated but responsive to erythropoietin therapy in renal disease. *Kidney Int* 2009; **75**: 976–981.
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Response to 'Plasma hepcidin levels are elevated but responsive to erythropoietin therapy in renal disease'

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As Morelle *et al.*[1] point out, one might expect to see a reduction in plasma hepcidin levels post dialysis—on size considerations alone, perhaps a 20–30% reduction would be anticipated, but in the six patients studied in our report,[2] no reduction was observed. These patients were dialyzed for 4 h using 2.1 m^2 low-flux acetate membranes with a minimum ultrafiltrate volume of 21, delivering a dialysis dose (spKt/V) of over 1.5 in all patients.

Although this may simply reflect a type 2 error—with a sample of six patients a small reduction might not be detected (95% confidence interval = 80–120% for the post–pre dialysis hepcidin ratio)—other explanations should not be overlooked. For example, hepcidin might be secreted into the circulation in appreciable quantities during dialysis, or, alternatively, clearance may be less than expected, because of aggregation or binding to larger plasma proteins such as alpha-2-macroglobulin.[3]

The inverse relationship between cholesterol and hepcidin was not explained by statin use, which was not predictive of hepcidin level in bivariate or multivariate analysis. Any cholesterol association is perhaps more likely to result from the inverse correlation between cholesterol and interleukin-6, although it should be emphasized that these associations, based on multiple comparisons, are relatively weak.

1. Morelle J, Labriola L, Jadoul M. Plasma hepcidin levels are elevated but responsive to erythropoietin therapy in renal disease. *Kidney Int* 2009; 1116.
2. Ashby DR, Gale DP, Busbridge M *et al.* Plasma hepcidin levels are elevated but responsive to erythropoietin therapy in renal disease. *Kidney Int* 2009; **75**: 976–981.
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