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Hepcidin levels in patients with renal disease

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To the Editor: In their interesting paper, Ashby *et al.*[1] report significantly elevated levels of serum hepcidin in patients with chronic kidney disease (CKD). Although serum ferritin was the main determinant of hepcidin levels, a significant negative correlation with glomerular filtration rate (GFR) remained in multivariate regression analysis. These data thus suggest that in patients with CKD the low GFR may contribute to higher levels of hepcidin, thus contributing to the anemia of CKD. Of note, the authors used a novel immunoassay that measures total hepcidin, not only that consisting of bioactive hepcidin-25 but also of the smaller inactive isoform hepcidin-20. We have measured serum hepcidin levels in patients with CKD using a mass spectrometry-based assay that quantifies hepcidin-25 and hepcidin-20 separately.[2] Serum hepcidin-25 levels were elevated in patients with CKD and correlated with serum ferritin.[3] However, in multiple regression analysis GFR was not a significant independent predictor of hepcidin-25. In contrast, we observed a significant independent negative relation between GFR and both hepcidin-20 and total hepcidin. We therefore conclude that the conclusion of Ashby *et al.* may not be applicable to the biologically active hepcidin-25 isoform. The biological relevance of the relationship between total hepcidin and GFR is questionable.

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Response to 'Hepcidin levels in patients with renal disease'

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The presence in the circulation of biologically inactive fragments of hepcidin-25 is an important issue, and the ability to distinguish between them might be an advantage of assays based on mass spectrometry. Peters *et al.*[1] comment that they also found elevated circulating hepcidin-25 in chronic kidney disease, but that only hepcidin-20 was independently correlated with glomerular filtration rate, and conclude that our measurements are distorted by the inclusion of hepcidin-20.

However, the immunoassay we used does not measure total hepcidin. Hepcidin-20 crossreactivity with this antibody is $<10\%$, and as described in Figure 3 of our report, over 90% of the immunoreactivity in renal failure samples was due to a single species chromatographically identical to hepcidin-25.[2] We have also completed a method comparison study in which measurements using this immunoassay and using a mass spectrometry–based method[3] were in close agreement ($R=0.96$, $n=99$, Figure 1).

We offer three alternative explanations for their failure to identify glomerular filtration rate as an independent predictor of hepcidin-25. First, there may be qualitative differences between the populations studied (for example, due to comorbidities). A second possibility is a type 1 error in our study, although the significance of glomerular

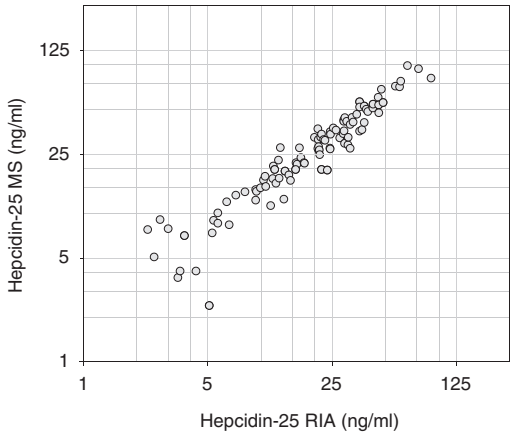

Figure 1 | Agreement between hepcidin-25 measurements by radioimmunoassay (RIA) and mass spectrometry (MS) methods ($n=99$).