be used before more extensive investigations of patients with unexplained hypoalbuminemia and edema.[6–9]

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The utility of multivariate analysis in the study of hepcidin

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To the Editor: In their recent publication, Ashby *et al.*[1] examined serum hepcidin levels in chronic kidney disease (CKD) using a novel immunoassay. Although they found a positive correlation between hepcidin and ferritin in non-dialysis CKD patients, they did not identify a correlation in patients on hemodialysis with univariate analysis. This was attributed to a lack of variation in ferritin levels, which were high because of 'target-driven treatment with intravenous iron'.

However, in Table 1 they present a multivariate model adjusted for erythropoietin and hemoglobin, which shows a correlation between hepcidin and ferritin ($\beta = 0.247$, $P = 0.013$) in the hemodialysis group. Similarly, the authors state that no relationship was seen between hepcidin and interleukin-6 levels, but the same multivariate model shows a correlation between the two variables ($\beta = 0.195$, $P = 0.054$).

These correlations seen in the multivariate model by Ashby *et al.* are in line with previous results indicating that hepcidin production is increased by iron loading and inflammation.[2] Since their publication, using another immunoassay, we have found with multivariate analysis a positive correlation between hepcidin and both high-sensitivity C-reactive protein and ferritin in pediatric and adult CKD patients.[3] Thus, given its complex regulation, multivariate analysis may be necessary when attempting to examine relationships between hepcidin and markers of iron status, inflammation and erythropoiesis.

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Response to 'The utility of multivariate analysis in the study of hepcidin'

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Multiple linear regression (MLR) is a useful technique for examining the manner in which a set of explanatory variables account for differences in hepcidin levels within a group. Zairitsky and Young[1] point out that significant partial correlations emerged in our MLR model for predictors that were not associated with hepcidin in bivariate analyses, and suggest that our underinterpretation is due to insufficient reliance on MLR.

Figure 4 of our report demonstrates clearly the influence of ferritin and iron loading on hepcidin in renal failure and dialysis patients, and indicates the ferritin clustering (due to the regular use of intravenous iron to ensure a minimum ferritin of 400 ng/ml), which explains the poor correlation within the dialysis group.[2] The MLR model adjusted for hemoglobin and erythropoietin does hint at other possible influences, but these were not incorporated into the model, as several mutually redundant predictors were present, and further inclusion produced little overall improvement in the model. For both ferritin and interleukin-6, it is clear that lack of influence *within* the group in no way implies lack of effect *on* the group.

MLR has significant drawbacks, being highly dependent on the set of explanatory variables available and the simultaneous interpretation of multiple *P*-values. Over-reliance, particularly when the ratio of observations to predictors is low, may lead to spurious associations while