Hepcidin—a well-known iron biomarker with prognostic implications in chronic kidney disease

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‘There is a great difference between knowing and understanding: you can know a lot about something and not really understand it’. Charles Kettering

Studying hepcidin in humans is en vogue as demonstrated by an increasing number of publications addressing this key hormone of iron homeostasis over the last decade. As a key regulator of iron transport, hepcidin has been clearly implicated in the pathogenesis of anaemia in chronic kidney disease (CKD), but a more complex pathophysiology is beginning to emerge in which altered iron biology contributes more widely to the complications of uraemia. In CKD, anaemia is caused by a variety of mechanisms, including erythropoietin (EPO) deficiency and resistance and impaired iron metabolism [1]. A (chronic) inflammatory state has been shown to be involved, in part, as a cause or as a consequence of these processes [2]. In particular, disordered iron transport caused by inflammation may accelerate arterial disease, for example by increasing arterial stiffness, thus further enhancing the risk for cardiovascular (CV) events in CKD patients [2–5]. In this issue of Nephrology, Dialysis Transplantation, Neelke van der Weerd and colleagues present intriguing epidemiological data linking hepcidin levels with CV endpoints in haemodialysis (HD) patients [6].

The first reports about hepcidin described its antibacterial and antifungal activities in serum and urine [7, 8], but subsequently focus shifted as its important role in iron metabolism was discovered. Hepcidin 25, an active metabolite, is the key regulator of iron transport, governing intestinal absorption as well as release from the reticuloendothelial system, by its action on the iron export channel, ferroportin: hepcidin leads to internalization of ferroportin, which results in reduced plasma iron and therefore diminished iron availability. Hepcidin synthesis and release themselves are regulated by changes in iron storage, hypoxia and erythropoiesis [9–11]. Although hepcidin can be considered as an acute-phase protein [12] in particular in infectious diseases, levels of the hormone are also elevated in chronic (low grade) inflammation [9, 13]. Hepcidin levels have been described in association with markers of inflammation (e.g. C-reactive protein and interleukin-6), anaemia (e.g. haemoglobin and endogenous EPO) and most strongly with iron status (e.g. ferritin). Both anaemia and chronic inflammation are frequently detected in CKD, which explains the interest about hepcidin in nephrology and especially in the setting of renal anaemia.

While insufficient endogenous EPO synthesis in advanced CKD surely represents a major mechanism in the development of renal anaemia [14], a number of reports have shown that EPO levels frequently are within the 'normal' range despite being low for the degree of anaemia. The phenomenon of 'relative EPO deficiency' is perhaps better described as a 'blunted EPO response' and might be insufficient to cause anaemia without the contribution of other mechanisms [15–17]. Further insight comes from the anaemia of chronic disease, with which renal anaemia shares several pathomechanisms, including inflammation and ‘relative’ iron deficiency, that is, insufficient iron availability despite adequate iron stores. In a landmark review article by Weiss [11], these mechanisms were clearly depicted and considered as crucial for the development of anaemia of chronic diseases, which is also frequently described as anaemia of chronic inflammation. A number of publications over the last years have focused on these mechanisms, and a robust body of evidence is developing about the pathophysiologic role of hepcidin in disorders of iron metabolism including renal anaemia. More recently emerging are a small number of studies suggesting a role for hepcidin in the development of CV disease, and as a biomarker and prognostic factor for clinical outcomes, in particular in CKD.
The United States Food and Drug Administration defines a biomarker as a laboratory measurement that reflects the activity of a disease process [18] whereas a prognostic factor represents a characteristic that is related to prognosis and the risk for achieving certain endpoints [19]. In the last years, we have seen an increasing interest in prediction models to assess the patient’s risk for achieving a certain outcome. Usually, a limited number of variables are combined in a model that might be translated into a clinically useful score. Biomarkers were thought to play crucial roles, but frequently few clinical variables carry most of the individual’s risk: for example, baseline glomerular filtration rate and proteinuria are sufficient to determine most of a patient’s risk of developing end-stage renal disease (ESRD) [20]; moreover, age and albumin represent the key variables predicting mortality in patients on renal replacement therapy [21]. It is of note that variables in a predictive model often summarize various processes that are related to the outcome, e.g. albumin can be seen as a marker of inflammation as well as nutrition, and it is not always necessary to ultimately understand these pathways, although it usually makes things easier to interpret. In most cases, the accuracy of a predictive model is displayed as the C-statistic of the model, which can be interpreted similarly as the Area Under the Receiver Operator Curve: it describes the probability that the model will assign the higher risk to the patient who achieved the outcome compared with the patient who did not. The C-statistic of a perfectly discriminating model would have values of close to 1, while 0.5 would describe a model that is no more accurate as flipping a coin [22]. However, to predict the individual’s risk more precisely, additional variables, e.g. biomarkers, can be implemented in the model. These may not markedly increase the C-statistic, but their incremental value to the model can be assessed by other markers of model performance as also suggested by current recommendations [23]: these include measures of calibration, or the integrated discrimination improvement and net reclassification improvement. However, these details about the prognostic value of certain biomarkers are rarely presented in the literature, although the number of models reporting these details is increasing [24]. Moreover, even if a biomarker proves to be of promising prognostic value, its role in clinical routine is also determined by weighing the additional cost of frequently expensive measurement against its benefit, that is, its evidence to modify treatment decisions. It would be desirable in an area in which a vast number of newly discovered biomarkers are presented in the literature and at scientific meetings, if these markers get rigorously tested regarding their prognostic ability as well as their clinical impact; unfortunately, these aspects are rarely investigated and reported.

Coming back to hepcidin and its nature as a biomarker and potentially a relevant prognostic marker, the hypothesis that hepcidin might be associated with important clinical events seems intuitive: anaemia and chronic inflammation are common in CKD and ESRD, and both are related to worse clinical outcomes such as mortality, CV events and progression of CKD to ESRD. On the other hand, hepcidin itself is closely related to anaemia, chronic inflammation and CKD.

In the current report [6], van der Weerd et al. describe hepcidin 25 as a predictor of mortality and CV events in HD patients enrolled in the CONvective TRAnsport STudy [25]. In this trial, a total of 714 prevalent HD patients had been randomized to either continue low-flux HD treatment or start postdilution online haemodiafiltration. Primary outcome was all-cause mortality, and no significant effect of the assigned treatments in the intention to treat analysis was detected. Anaemia management and fatal and nonfatal CV events were secondary outcomes, and blood samples were collected in centres with adequate sample processing and storage logistics. Thus, for the current analysis, a subset of 405 patients was considered in whom hepcidin 25 was measured at baseline. Inlogically constructed Cox proportional hazards models, the associations of hepcidin levels with mortality and CV events were investigated. In univariate analyses, hepcidin was related to both outcomes. However, after stepwise adjustment for comorbidities and anaemia parameters, the relationship between hepcidin and mortality disappeared, in particular when controlling for ferritin and C-reactive protein. On the other hand, the association of hepcidin with CV events appeared to strengthen after multivariate adjustment, although the incremental predictive value of adding hepcidin to the model was not reported. The authors interpret their results as evidence for the involvement of hepcidin and disordered iron metabolism in the pathophysiology of renal vascular disease, pointing out that its role as an acute-phase reactant would confound any consequent association with mortality due to the large number of deaths due to infection in the study. Thus, the mortality effect seems to be mainly driven by classical markers of inflammation and iron status, whereas for CV events, hepcidin appears to be telling us something not covered by conventional markers.

Although hepcidin was measured with the gold-standard mass spectrometry, one could argue that the authors have put too large a number of covariates in the models and finding associations by chance is surely possible. However, one of the purposes of the study must be to generate hypotheses and to try to understand the relationship between hepcidin and hard clinical outcomes. The use of hepcidin determined at a single time-point might also be considered a weakness, as substantial intra-individual variability of hepcidin levels has been described in HD patients even when measured with mass spectrometry [26], but the statistical modelling of complicated and time-dependent processes, which are further modified by a multitude of therapeutic regimens to correct anaemia, represents an ambitious task.

The study clearly adds valuable evidence to the hypothesis that abnormal hepcidin signalling is at the centre of a pathophysiological syndrome linking anaemia with vascular disease and early mortality in dialysis patients. It complements and extends previous cross-sectional studies linking hepcidin with vascular pathology [3], and longitudinal evidence that baseline hepcidin predicts the subsequent development of anaemia in CKD [27]. Hepcidin measurement is clearly helpful in picking out a certain phenotype among HD patients, but whether it has true prognostic value remains undetermined. But perhaps the more pertinent question is whether anything could be done about a raised hepcidin level: could reduced vascular disease and clinical benefit be achieved by therapies aimed at reducing hepcidin signalling?

There are a number of possible strategies, in various stages of development, by which hepcidin could be inhibited. For
example, in animal models of inflammatory anaemia, haemoglobin has been improved using antagonists of BMPs (bone morphogenetic proteins), which form an integral part of the signal regulating hepcidin according to iron status, and by monoclonal antibodies directed against hepcidin [28]. Further developed are HIF prolyl hydroxylase inhibitors, which stabilize HIF thus acting as a ‘hypoxia mimetic’ leading to a number of transcriptional changes including hepcidin suppression [29]. Some of these have reached phase 2 clinical studies in dialysis patients and appear to be effective in treating anaemia in addition to, or perhaps because of, a reduction in hepcidin. Although hepcidin is a uremic toxin thought to be removed during dialysis, so far no study has addressed the effect of a dialytic strategy to enhance hepcidin removal, but hepcidin clearance could be responsible for the reported association between dialysis adequacy and EPO requirement [30]. Unwittingly, the most studied method of hepcidin reduction is by therapeutic EPO, which has been shown to reduce circulating hepcidin [31, 32], although the mechanism by which this occurs, thought to be a marrow-derived factor, is still unknown. However, as is well known, improved clinical outcomes were not seen in a number of recent interventional studies of increased EPO dosing [33]. But this does not count as evidence against van der Weerd’s hypothesis linking hepcidin with CV events. Rather it reminds us that in the clinical arena, a biomarker is only a number and that the method by which a biomarker is reduced or inhibited may be more important than the effect on the number itself. This is particularly so when the link between the biomarker and the pathological process is so poorly understood: in the case of hepcidin then, future research should focus on the process behind the clinical outcome and establishing whether enhanced dialysis or administration of an antagonist could have any influence on this pathological sequence.

There is of course much to learn regarding the overlapping mechanisms of anaemia and vascular disease in CKD patients. In the coming years, doubtless we will see many advances in the characterization of this syndrome, and as results accumulate, perhaps we will watch hepcidin evolve from a biomarker of anaemia to a prognostic factor for clinical events. As our knowledge certainly increases, so hopefully will our understanding.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part.

(See related article by van der Weerd et al. Hepcidin-25 is related to cardiovascular events in chronic haemodialysis patients. Nephrol Dial Transplant 2013; 28: 3062–3071.)

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Received for publication: 8.10.2013; Accepted in revised form: 25.6.2013

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