Iron deficiency in patients with chronic kidney disease requiring hemodialysis: do inflammation and overexpressed hepcidin contribute significantly?

To the Editor  Chronic kidney disease (CKD) and heart failure (HF) are the prime examples where the concomitant inflammation interferes with iron metabolism and, as a consequence, iron deficiency in such clinical settings is the combination of absolute iron deficiency (depleted iron stores) and functional iron deficiency (preserved iron stores with deranged iron redistribution from target cells to reticuloendothelial cells). 1,2

The study reported by Małyszko et al. 3 draws our attention to functional iron deficiency (defined as ferritin >200 ng/ml with transferrin saturation [TSAT] <20%), which is common in patients with advanced CKD on hemodialysis (with the prevalence reaching almost 25%), and indeed is accompanied by high levels of circulating inflammatory molecules (interleukin 6, high-sensitivity C-reactive protein). These results are in line with the other studies in patients with CKD, both those requiring and not requiring hemodialysis. 4 However, this issue is not so obvious, as one may presume. For example, contrary to expectations, among patients with systolic HF, iron deficiency is in most cases absolute, not being related to inflammation, and accompanied by low (rather than high) circulating hepcidin. 5 It is also quite surprising that in the study by Małyszko et al., 3 there have been no differences in serum soluble transferrin receptor (sTfR) between patients with CKD with vs. without functional iron deficiency. Circulating sTfR is a biomarker of the best accuracy. It reflects the depleted amount of intracellular iron, which is available for cellular metabolism. 6 TSAT is the direct measure of the circulating iron pool used for the diagnosis of iron deficiency in case of inconclusive ferritin values. 7 Importantly, although TSAT is suggested to reflect the amount of iron in the peripheral tissues, 1 the direct evidence supporting this view is missing.

Hepcidin is an evolutionary conservative molecule, and as such, it plays several functions critical for homeostasis maintenance, including the systemic control of iron metabolism and immune response. 8 Hepcidin detected in peripheral blood originates mainly from hepatocytes, and its expression is increased during inflammation and reduced during depleted iron stores, hypoxia, and ineffective erythropoiesis. Circulating hepcidin interacts with its specific receptor (ferroportin) on target cells. Through this mechanism, hepcidin decreases intestinal iron absorption and diverts iron from the circulation into the reticuloendothelial system, and as a consequence diminishes iron availability to iron-metabolizing cells. 8

The observation that iron deficiency in patients with CKD on hemodialysis is predominantly functional, related to inflammation, and accompanied by high circulating hepcidin provides evidence that is relevant in the context of the applied treatment aiming to restore normal iron status. The limitation of the study is the small number of examined patients with CKD, which implies that the results, particularly those of the multivariable analyses, should be interpreted with caution. Also, the cross-sectional design of the study does not allow to conclude directly from the observed associations about the causal relationships. Nevertheless, the presence of functional iron deficiency implies that instead of iron supplementation, therapeutic strategies should focus on either diminishing inflammatory processes, the inhibition of hepcidin secretion, or blocking its biological action (using for example anti-hepcidin antibodies).

In our opinion, the assessment of the other molecules in the context of the iron status (growth differentiation factor 15, bone morphogenetic protein 6) has a less established background. Firstly, these molecules participate mainly in the local regulation of iron metabolism (sometimes differently in distinct tissues), 9 and their circulating pool does not accurately reflect the local tissue status. Secondly and most importantly, these molecules are involved in several cellular...
pathways, and their circulating level cannot be specifically associated only with the iron status. These facts are particularly important when assessing these molecules in a heterogeneous population of patients with CKD.

Although the authors have demonstrated the prevalence of functional iron deficiency in patients with CKD on hemodialysis, they have not answered the question that is clinically important here. Namely, are there any clinical and prognostic consequences of functional iron deficiency in this group of patients? In this context, it should be emphasized that limited iron availability accompanying functional iron deficiency results, for example, in erythropoietin resistance. Undoubtedly, these intriguing issues warrant further studies.

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**Authors’ reply**  The idea of our study was to draw attention to the problem of functional iron deficiency in dialyzed population. In our previous studies, we have shown an increased hepcidin levels in these patients. The population of patients with CKD is much more heterogeneous than that with chronic heart failure, due to different diseases leading to end-stage renal disease. Probably this is why iron deficiency is in most cases absolute, not being related to inflammation and accompanied by low (rather than high) circulating hepcidin, as reported by Jankowska et al. among patients with systolic heart failure. As per definition, CKD is a chronic disease, and discrepancies in ferritin concentrations between normal subjects and CKD patients are partly due to the fact that ferritin is an acute-phase reactant and CKD is a subclinical inflammatory state, while in normal subjects these values of ferritin are within the normal range.

It is now recognized that functional iron deficiency may exist among patients with renal failure; this is characterized by the presence of adequate iron stores as defined by the conventional criteria, but with inability to sufficiently mobilize this iron to adequately support erythropoiesis with the administration of erythropoietin. In this setting, an inadequate amount of iron is released from the liver and other storage sites. Among such patients, the serum ferritin level is either normal or elevated, but TSAT typically falls to about 20% or below. It is clinically important to distinguish functional iron deficiency, which usually responds to iron therapy, from inflammatory iron block, which does not. The inflammatory iron block occurs among patients with refractory anemia largely due to an underlying inflammatory state. Unfortunately, with both functional deficiency and inflammatory block, the transferrin saturation is less than 20% and the ferritin level is elevated (between 100 and 800 ng/ml).

In patients with acute or chronic inflammatory conditions, the diagnosis of iron deficiency or functional iron deficiency is particularly challenging because most of the biochemical markers for iron metabolism are affected by the acute-phase reaction. The response to erythropoietin or parenteral iron may help distinguish between these two possibilities. In patients with functional deficiency, but not with inflammatory iron block, ferritin levels may decrease with erythropoietin administration. Inflammatory block is also most likely present if the administration of intravenous iron is associated with a progressive increase in the ferritin concentration rather than with increased erythropoiesis. Based on these findings, we would like to stress the clinical importance of functional iron deficiency to introduce the appropriate treatment strategies. It has already been emphasized that limited iron availability accompanying functional iron deficiency results for example in erythropoietin resistance as per definition of functional iron deficiency. Our data support the concept that hemodialysis patients are...
inflamed, and this population should be investigated for underlying and potentially reversible causes. More adequate dialysis with more compatible membranes should also be taken into account in these patients to diminish the inflammation; however, there is still no hard evidence for this approach.

In our study, we did not observe a difference in sTfR between the 2 groups of HD patients. It is known that plasma iron transport is carried out by transferrin, which delivers iron into cells through its interaction with a specific membrane receptor – the transferrin receptor. In the presence of iron deficiency, the sTfR concentration in serum rises, even before the hemoglobin concentration is significantly depressed. Therefore, the sTfR concentration can describe the functional iron status, while ferritin reflects the iron storage status. Studies have shown that the level of sTfR is markedly elevated in iron deficiency anemia but remains normal in anemia due to chronic inflammation without iron deficiency and thus may be of considerable help in differentiating between iron deficiency anemia and anemia of chronic disease. However, some data have demonstrated that sTfR offers little advantage over conventional laboratory indicators of the iron status and might not assess the iron status of patients with anemia of chronic disease. Lee et al. demonstrated that sTfR is not superior to ferritin for detecting iron depletion, confirming the results previously obtained by Mast et al. We might also think about the effect of pH and drugs commonly used by CKD population on the possible secretion of sTfR into the circulation. Lack of difference in serum sTfR between the two studied groups might be due to its low sensitivity and specificity in the assessment of iron status in hemodialysis population.

Therefore, the assessment of sTfR was not introduced to the armamentarium of measurement of iron status on daily basis. Moreover, the latest Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on anemia treatment do not recommend the assessment of sTfR (it is cleared by the kidneys as well). Since there is no perfect marker of the iron status, the search for the novel ones continues. In everyday clinical practice, we still use TSAT and ferritin as recommended by the latest KDIGO guidelines being fully aware of their limitations, which are perfectly recognized by the nephrology community.

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