Title
Moderately high serum ferritin concentration is not a sign of iron overload in dialysis patients

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LETTERS TO THE EDITOR

Moderately high serum ferritin concentration is not a sign of iron overload in dialysis patients

To the Editor: The review of Eschbach and Adamson [1] maintained that increased serum ferritin concentration is a sign of iron overload and a risk factor for infection in dialysis patients. Whereas a low serum ferritin level is reported to be highly specific in diagnosing iron deficiency [2], the accuracy of a high serum ferritin level to diagnose iron overload has been questioned. In a previous study [2], we examined bone marrow iron stores (scored 0 to 4+) in 24 uremic patients and showed that serum ferritin values were significantly lower only in patients with completely depleted bone marrow (score zero), while four other groups had similar ferritin levels (Fig. 1A). The average bone marrow iron scores in four ferritin "quartiles" were exceptionally low in the lowest quartile but no difference was observed among the other three higher quartiles (Fig. 1B). Pearson correlation coefficients of log ferritin and transferrin, albumin, and C-reactive protein (CRP) were −0.72, −0.54 and +0.41, respectively ($P < 0.05$). These results denote that a high serum ferritin is not a reliable indicator of iron overload, but may instead represent an acute phase reactant as reflected by increased CRP.

Recently, Gunnell et al showed that erythropoietin resistance occurred in the context of high ferritin and low transferrin levels, the pattern expected in the acute-phase response, not in iron overload [3]. We showed that sick, malnourished, dialysis patients had an increased serum ferritin and decreased transferrin levels and required higher doses of erythropoietin [4]. More recently, we found that increased serum ferritin is a predictor of mortality in dialysis patients and has a relative risk of death of 1.80 (95% CI: 1.04–3.11) (abstract; Kalantar-Zadeh K et al., *Am J Kidney Dis* 33:A30, 1997. Thus, the impression that an increased serum ferritin is a risk factor for infection might be flawed and based on cross-sectional observations that confirm a strong "association" between serum ferritin and the degree of "sickness" without any proof of a "cause-effect" relationship. Therefore, iron stores should not be evaluated solely on the basis of serum ferritin and abnormally high serum ferritin concentrations may not be a reliable indication for withholding iron administration in uremic patients.

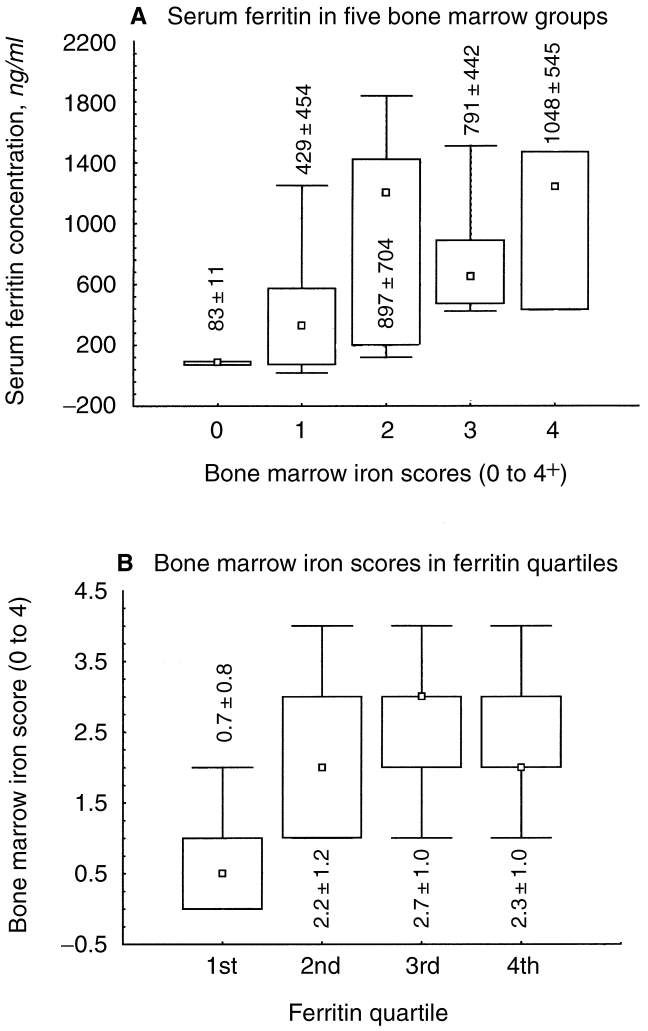

Fig. 1. Box and Whisker plot. (*A*) Serum ferritin concentrations in 5 groups of bone marrow iron scores (0 to 4+). (*B*) Bone marrow iron scores in 4 ferritin quartiles. Symbols are: (⊥) min-max; (▭) 25%–75%; (□) median value.

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Authors' Reply

We agree with everything that Drs. Kalantar-Zadeh, Luft and Humphreys state in their letter, with the exception of the first sentence. Our review did not maintain that an increased serum ferritin concentration is a risk factor for infection in dialysis patients. We went to great lengths to question critically whether there is an association between infection and iron overload, showing that increased infection may have occurred in the pre-recombinant human erythropoietin era when transfusion-induced immunological suppression and severe-moderate anemia were common, both of which are risk factors for infection. Since the advent of erythropoietin therapy and partial correction of the anemia, with elimination of red blood cell transfusions, there is no evidence that links serum ferritin levels <1000 ng/dl, associated with transferrin saturation levels of <50%, with an increased risk for infection.

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Errors in reported association between Tamm-Horsfall protein and IgG

To the Editor: We regret to inform you that we have detected calculation errors affecting the data in our article "Tamm-Horsfall glycoprotein binds IgG with high affinity" [1]. The data for total IgG and bound IgG were entered in the least squares program as pmol; however, the calculations and output assumed these values were as concentrations and thus were interpreted as pM. In reality, the amount of IgG in pmol was present in 50 μl of sample and thus the assumed concentration in these samples was off by a factor of 20,000 (1,000 ml/0.05 ml = 20,000). Re-evaluating the data correctly entered in the least squares program as nM (instead of pmol) results in affinity constants 20,000 times less strong. Because of this error, a few sentences in the article need to be changed.

1. In the abstract, the fifth sentence should read: "Analysis of the ELISA data identified the presence of two sets of binding sites: a high affinity site (K_d 10^{-8} to 10^{-9} M) and a lower affinity site (K_d 10^{-6} to 10^{-7} M)."
2. On page 1017, the first sentence in column two should be changed to: "The K_d of the high affinity sites ranged from 10^{-9} to 10^{-8} M, while the low affinity site K_d was approximately 10^{-7} to 10^{-6} M."
3. The next paragraph on page 1017 should read: "Using a comparable ELISA, hTHP bound human IgG in a dose-dependent manner. The hTHP/human IgG binding data were best described by one binding site with a K_d of 10^{-7} M."
4. Finally, the caption for Figure 6 should contain the new binding parameters: $K_{d1} = 6.7 \times 10^{-7}$ M, $K_{d2} = 1.4 \times 10^{-8}$ M, $A_1 = 1.2 \times 10^{-8}$ M, and $A_2 = 4.8 \times 10^{-9}$ M.

While these new binding constants indicate a weaker association between THP and IgG than originally thought, the basic evaluation of the significance of this association remains unchanged from that presented in the article.

We sincerely apologize for the errors in the binding constants originally presented.

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