Limitation of serum ferritin in the monitoring of chronic kidney failure

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Abstract:
Assessment of iron status is essential in the management of chronic kidney failure; nevertheless, the assay of conventional markers often leads to questionable results. This work aims to show the disproportionate elevation of serum ferritin levels in chronic kidney failure patients.

This is a six-month retrospective study. We evaluated iron metabolism, C-reactive protein (CRP), and hemogram determination in 2 groups of patients. The first group consisted of 200 chronic kidney failure patients with anemia, the second group consisted of 100 anemic patients with normal kidney function, no inflammation, infection or tumoral disease.

The average age in the first group was 60.2±14.08. The mean ferritin level was 385.25ng/mL ±360.52. Serum ferritin level was ≤500 ng/mL in 119 patients, between 500 and 1000 ng/mL in 47 patients, and greater or equal to 1000ng/mL in 34 patients. As for the second group, the mean ferritin level was 28.20ng/mL ±72.13. The prevalence of iron overload was significant in group 1(40%). However, no case of overload was reported in the 2nd group.

Through the results of this work, we deduced that there is a statistically significant correlation between chronic kidney failure and serum ferritin increase.

Keywords: Serum ferritin, Iron, Anemia, Chronic kidney failure, Inflammation

I. Introduction:
Iron deficiency and iron-deficiency anemia are global health problems and common medical conditions seen in everyday clinical practice (1). Timely detection and treatment are important because of the critical role played by iron in the function of all organ systems (2), including respiration, energy production, DNA synthesis, and cell proliferation. Iron deficiency, even in the absence of anemia, can be debilitating, and exacerbate any underlying chronic disease, leading to increased morbidity and mortality. Iron deficiency is frequently concomitant with chronic inflammatory disease; however, iron deficiency treatment is often overlooked, partially due to the heterogeneity among clinical practice guidelines(3). Iron deficiency is estimated to affect 37–61% of patients with chronic heart failure (CHF), 24–85% of patients with chronic kidney disease (CKD) and 13–90% of patients with inflammatory bowel disease (IBD) (4)(5)(6).

Monitoring the iron status of patients with chronic kidney failure only with conventional markers, such as serum ferritin and transferrin saturation, leads to questionable results because of the frequent coexistence of chronic inflammation, infection, and malnutrition(7)(8)(9). These comorbid conditions generally affect the commonly used indices of body iron stores(10). Therefore, any interpretation of a given serum ferritin level in these patients needs to take into account the possible role of factors other than the status of iron repletion (11)(12)(13)(14).

In normal circumstances, iron status can usually be assessed adequately by measuring serum levels of ferritin. In the presence of pro-inflammatory stimuli, however, the diagnosis of iron deficiency is more complex. Understanding the nature of serum ferritin and, particularly, how levels of serum ferritin are influenced by inflammation is key to successful diagnosis in this context(15)(16).

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The objective of this paper was to study an extended iron status in a population of kidney failure patients, and to demonstrate the disproportionate increase of serum ferritin values and its repercussions on the management of iron deficiency in such patients.

II. Materials and methods:

1. Study population

This is a six-month retrospective, descriptive and analytical study. We evaluated iron metabolism in 2 groups of patients. The first group consisted of 200 patients suffering from chronic kidney failure with anemia. The underlying diseases were hypertension (73), diabetes mellitus (81), chronic glomerulonephritis (33), and other causes: lupus nephritis (11), neurologic bladder (2).

The second group consisted of 100 anemic patients with normal kidney function, no inflammation, infection or tumoral disease.

2. Biological parameters:

The hematological parameters were determined by means of Sysmex® XT 4000i on blood sample taken from plastic EDTA tubes.

For biochemical parameters the samples were analyzed on lithium heparin tubes from both hospitalized patients and outpatients. Blood for all sample measurements was drawn by venipuncture.

The parameters of the martial assessment, CRP (C Reactive Protein), albumin, transaminases were assayed on the Cobas® 6000 analyzer. Ferritin was evaluated by Electrochemiluminescence Assay.

Iron status was assessed by measuring serum iron, serum transferrin, total iron binding capacity (TIBC), transferrin saturation (TSAT), and serum ferritin.

In the first group, iron deficiency was defined as serum ferritin <150 ng/ml and TSAT <20%, while iron overload as serum ferritin >500ng/ml and TSA T >50%.

For the second group, a ferritin level <15-30 ng/ml is the best non-invasive test for iron deficiency(17). Patients were classified as having normal, deficient or overload status.

The cutoff levels of hemoglobin for diagnosis of anemia depend on age, sex and pregnancy(18) (table I).

| Age/Gender Groups         | Hb Below (g/dL) |
|---------------------------|-----------------|
| Children                  | <11.0           |
| 6 months to 4 years       |                 |
| 5 to 11 years             | <11.5           |
| 12 to 14 years            | <12.0           |
| Adults                    |                 |
| Non-pregnant women ≥15 years | <12.0       |
| Pregnant women ≥15 years  | <11.0           |
| Men ≥15 years             | <13.0           |

3. Ethical aspects:

After approval by the ethics committee, patient’s consent was obtained.

Funding of this study was from strictly institutional sources.

Respect for anonymity and confidentiality were taken into account during Data collection.

4. Statistics:

Results are expressed as averages +/- standard deviation. To compare 2 averages, we used Student's t-test. The results were considered significant at the 5% uncertainty level (p <0.05). Pearson's correlation coefficient was used for the analysis of relationships between martial status parameters, CRP, and kidney failure.

The data was entered and processed using SPSS 25.0 and Excel 2019 softwares.

III. Results:
The first group consisted of 111 men and 89 women, a sex ratio of 1.25. The mean age of our patients was 60.2 ± 14.08 (16-86). The second group consisted of 41 men and 59 women, a sex ratio of 0.69. The mean age was 37.62 ± 14.7 (16-64).

In the first group, the mean ferritin level was 385.25 ng/mL ± 360.52 (5.4-2000 ng/mL). The average hemoglobin level was 10.26 g/dL ± 2.1 (5.4-12.7 g/dL). The mean serum iron level was 7.1 ± 3.1 μmol/L and the average CRP was 23.34 ± 53.6 mg/L (Table II).

Serum ferritin level was ≤500 ng/mL in 119 patients, between 500 and 1000 ng/mL in 47 patients, and greater than or equal to 1000 ng/mL in 34 patients (Table III).

Regarding the second group, it consisted of 41 men and 59 women, a sex ratio of 0.69. The mean age of our patients was 37.62 ± 14.7 (16-64). The average ferritin level was 28.20 ng/mL ± 72.13 (2-430 ng/mL). The average hemoglobin level was 10.95 g/dL ± 1.8 (6.9-12.8 g/dL). The mean serum iron level was 7.6 ± 3.2 μmol/L and the average CRP was 2.6 ± 1.64 mg/L.

The study of the hematological and martial parameters shows no important difference in hemoglobin nor serum iron levels between the 2 groups, whereas ferritinemia was 13 times higher in the 1st group (figure 1).

The prevalence of iron overload was high in group 1, 40% (81/200 patients). However, no case of overload was reported in our 2nd group.

In our series, the study of the correlation between the values of ferritinemia, renal outcome and influencing factors such as CRP (table IV) showed a statistically significant correlation between renal failure and serum ferritin increase, with a "p" value of 0.01, and a statistically significant correlation between ferritin and CRP levels in patients with renal impairment, with a "p" value of 0.01.

### Table II: Hematological and iron profile of studied patients in group 1:

| Parameters                   | Averages          |
|------------------------------|-------------------|
| Serum iron (umol/L)          | 7.1 ± 3.1         |
| Serum ferritin (ng/mL)       | 385.25 ± 360.52   |
| Transferrin (g/L)            | 4.05 ± 10.98      |
| TIBC (umol/L)                | 46.85 ± 9.1       |
| TSAT (%)                     | 26 ± 4.35         |
| Hemoglobin (g/dL)            | 10.26 ± 2.1       |
| MCV (fl)                     | 92.44 ± 7.45      |
| MCH (pg)                     | 28.86 ± 3.07      |
| MCHC (g/dL)                  | 31.16 ± 1.22      |

### Table III: Distribution of ferritin and hemoglobin levels in group 1

|                  | Ferritine (ng/mL) | Hemoglobine average (g/dL) | Pourcentage (%) |
|------------------|-------------------|-----------------------------|-----------------|
| Group a          | ≤500              | 10.42                       | 59.5%           |
| Group b          | 500 to 1000       | 9.93                        | 23.5%           |
| Group c          | > 1000            | 10.45                       | 17%             |
| Total            | 385.25            | 10.26                       | 100%            |

### Table IV: Study of the relationship between CRP and ferritin in group 1:

| Breakdown of anomalies | CRP < 6mg/L | CRP > 6mg/L |
|------------------------|-------------|-------------|
| Group a                | 65          | 54          |
| Group b                | 17          | 30          |
| Group c                | 11          | 23          |
| Total                  | 93          | 107         |
Figure 1: Comparison of ferritin, hemoglobin and serum iron levels in both groups

IV. Discussion:

The management of patients with chronic renal failure, particularly the monitoring of their iron deficiency can be difficult. Indeed, the clinical significance of serum ferritin in monitoring iron status has become unreliable. Due to the influence of the complex malnutrition-inflammation syndrome, several authors have suggested to discontinue the use of serum ferritin as an indicator of iron stores in these patients (19).

Ferritin is a 450 kDa protein comprising 24 apoferritin monomers that associate to form a hollow spherical particle. Up to 4000 atoms of iron can bind in the sphere where they are stored as Fe3+ ions. In human cells, two subunits of ferritin exist; light (L) and heavy (H); most tissue ferritin molecules are a heterogenous mixture varying proportions of the two subunits (20). In fact, ferritin can be considered both as part of a group of iron-regulating proteins, as well as a member of the protein family that orchestrates the system of cellular defense against stress and inflammation (21). In addition, the effect of iron has been shown to be specific to the L-ferritin subunit, while the effects of inflammation, oxidative stress and cytokines are specific to the H-subunit.

Circulating ferritin is normally predominantly in the L form, and is not iron bearing. The H-subunit is thought to play a role in the rapid detoxification of iron due to its ferroxidase activity, which oxidizes iron to the Fe(III) form for deposition within the core, whereas the L-subunit facilitates iron nucleation, mineralization, and long-term iron storage (22)(23)(24). In vivo, a specific cell type synthesizes a specific ratio of H-ferritin and L-ferritin protein subunits during differentiation; the H:L protein subunit ratio is usually stable, except during chronic iron overload or inflammation (25)(26)(27). Furthermore, Miler et al proved that TNF alpha induced H-ferritin mRNA independently of iron (10). Hence, serum ferritin can be elevated in inflammation.

Furthermore, patients with inflammatory conditions, like in this case chronic kidney failure patients, may have diminished iron stores, a situation described as “absolute iron deficiency”, due to low dietary iron intake, poor iron absorption, and/or blood loss. On the other hand, these patients may also suffer from “functional iron deficiency”, caused by elevated hepcidin levels, triggered by inflammatory cytokines such as IL-6 (2). Such combined conditions render the interpretation of erythrocyte indices and parameters of iron status challenging.

Our study found a statistically significant correlation between renal failure and serum ferritin increase, confirming prior reports (28)(10). We also found that a statistically significant correlation existed between serum ferritin and CRP concentrations. Serum CRP is a marker of inflammation that is a very common condition in chronic kidney failure patients. The CRP concentration is shown to be a predictor of cardiovascular disease and mortality in both the general population and chronic kidney disease patients (29). Another interesting finding of our current study was a significant association between both serum CRP and ferritin levels and the degree of severity of anemia, similar to previous reports (30)(31).
For these reasons and more, the use of other more sensitive diagnostic elements such as hepcidin, soluble transferrin receptors (sTFR), the percentage of circulating hypochromic red cells (HRC) and reticulocyte hemoglobin concentration (CHR) are recommended in the monitoring of chronic kidney failure patients. The HRC represents the percentage of RBCs containing low hemoglobin (32). This can be measured by using special analyzers introduced by Green (33).

The discovery of the iron regulatory hormone, hepcidin, in 2001, revolutionized our understanding of iron disorders and its measurement should advance the diagnosis and treatment of these conditions. Hepcidin plays a central role in maintaining iron homeostasis. The synthesis of hepcidin in the liver is regulated at the level of transcription by multiple stimuli intracellular and extracellular. Iron concentrations increase the transcription of hepcidin, as well as inflammation via interleukin 6 and TNF-alpha., while increased erythropoietic activity decreases the production of hepcidin. Thus, in the event of an inflammatory situation with a suspicion of an absolute iron deficiency associated, the dosage of hepcidin could confirm the absolute iron deficiency (collapsed hepcidin) or strongly suggest it (normal "abnormally" hepcidin); conversely, this assay could allow retaining the diagnosis of isolated functional martial deficiency (increased hepcidin)(34). However, to this day, there is no validated and inexpensive measure technique to be used in everyday clinical practice.

In summary, we found positive associations between increase serum ferritin, CRP as marker of inflammation, and chronic kidney failure. More studies are required to confirm our findings and to reexamine current guidelines on iron administration to chronic kidney failure patients.

V. Conclusion:

In total, these data constitute the typical illustration of the disturbances in the martial balance of chronic kidney failure. They demonstrate the need to be particularly vigilant in the identification of a martial state disorder, but also during intravenous iron prescriptions, and underline the interest of a complete martial assessment for a better interpretation of the results. Other parameters deserve to be tested for a better appreciation of the martial status of kidney failure patients on dialysis: hepcidin, soluble transferrin receptors, percentage of hypochromic cells and Hb content of reticulocytes.

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COMPETING INTERESTS:

• The authors declare that they have no competing interest.