Zinc Levels After Iron Supplementation in Patients With Chronic Kidney Disease

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Objective: The goal of this study was to evaluate the effects of iron supplementation on zinc distribution in nondialyzed chronic kidney disease (CKD) patients.

Design: Prospective nonrandomized observational study.

Setting: Outpatients of the Nephrology Division at Federal University of São Paulo.

Patients: Zinc and iron status of 38 nondialyzed patients (63% male; creatinine clearance, 34.5±13.3 mL/min/1.73 m^2) was evaluated before and after 3 intramuscular injections of 100 mg iron each.

Main outcome measures: The following parameters were analyzed: erythrocytes and plasma zinc, zinc protoporphyrin (ZPP), plasma ferritin, transferrin saturation (TFS), and total iron. The patients' diets were analyzed by the Association of Official Analytical Chemists method for macronutrients, and neutron activation analysis was used for iron and zinc concentration determinations.

Results: Ferritin and TFS increased from 86.3±67.5 ng/mL to 105.4±63.7 ng/mL and from 19.5±7.4% to 23.2±6.7% ($P < .05$), respectively, after iron supplementation. Absolute iron deficiency (ferritin <100 μg/L and TFS <20%) was present in 41% of the patients and decreased to 15.7% after iron treatment. In comparison with baseline values (76.4±16.7 μg/dL), there were no significant changes in plasma zinc levels, but after supplementation the number of patients with low plasma zinc levels decreased from 46.1% to 23.7% ($P = .08$). At baseline, erythrocyte zinc was 49.0±7.6 μg Zn/gHb, and 76.3% of the patients had high erythrocyte zinc concentration. After iron treatment, erythrocyte zinc decreased to 45.5±7.3 μg Zn/gHb ($P = .001$). No significant change was observed in ZPP concentration. The analysis of the diet showed energy and protein intakes of 26.2±7.1 kcal/kg/day and 0.89±0.2 g/kg/day, respectively, and a low intake of both iron and zinc.

Conclusions: This study suggests that iron deficiency may contribute to the inadequate distribution of zinc in patients with CKD and that iron supplementation may decrease the abnormal elevated erythrocyte zinc levels of these patients.

ZINC plays three well-known physiological roles—catalytic, structural, and regulatory. Symptoms of zinc deficiency are anorexia, impaired smell and taste, growth retardation, hypogonadism, skin lesions, and decreased cell-mediated immunity.[1]

Subnormal plasma zinc concentrations have been reported in patients with CKD, but it is not clear at present whether a low concentration of zinc in plasma is indicative of zinc deficiency in these patients because erythrocyte zinc concentration is frequently reported to be elevated.[2-4] Zinc depletion was suggested to play a role in the pathogenesis of some uremic symptoms such as testicular atrophy, immune impairment, and abnormalities of taste.[3]

Reduced erythropoietin production and iron deficiency are the main causes of anemia in this population. In the nondialytic stage of CKD, iron stores may be low because of a combination of reduced iron intake caused by anorexia, low-protein diet, reduced gastrointestinal absorption of iron, use of phosphate binders, increased gastrointestinal blood loss, proteinuria, and reduced bone marrow use of iron.[5,6]

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Supported by FAPESP.

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1051-2276/04/1403-0007$30.00/0

doi:10.1053/j.jrn.2004.04.006

Parameters such as hematocrit, hemoglobin, ferritin, and transferrin saturation are currently used to assess iron deficiency. More recently, however, zinc protoporphyrin (ZPP) has been proposed to be another valid marker in this setting because the concentration of ZPP is inversely proportional to that of plasma iron. ZPP concentration increases during iron deficiency, because zinc instead of iron is incorporated into the protoporphyrin IX ring of heme, leading to an increase in the concentration of red blood cell ZPP and consequently increasing zinc concentration in the erythrocyte.[7,8]

Some studies in hemodialyzed patients have found an association between ZPP levels and anemia parameters.[9–11] These observations suggest a possible link between iron and zinc metabolic abnormalities in patients with CKD so that iron deficiency could contribute to the abnormal distribution of zinc stores. Thus, we hypothesize that the correction of iron deficiency through iron supplementation could improve the abnormal zinc distribution in nondialyzed CKD patients.

Methods and Materials

Subjects

The study was performed on 38 nondialyzed CKD patients with moderate anemia (Hb<12.0 g/dL) treated at the outpatient clinic of the Division of Nephrology at Federal University of São Paulo. Subjects younger than 18 years old or suffering from diabetes mellitus or autoimmune, malignant, or infectious diseases were not admitted into the study. During the study protocol, all patients were instructed to eat approximately 35 kcal/kg/day and 0.6 g to 0.8 g/kg/day of protein. All patients received folic acid and vitamin B12 supplements, and no patient was taking zinc or iron supplements.

Body mass index was calculated as the body weight divided by the squared height (kg/m^2).[12] The overall compliance with dietary protein prescriptions has been assessed by calculation of protein equivalent of nitrogen appearance (PNA) using the Maroni formula.[13]

The study protocol was reviewed and approved by the Ethics Committee of the Federal University of São Paulo (UNIFESP). All patients signed an informed consent form.

Study Protocol

After an overnight fast, blood was collected in plastic, zinc-free tubes with sodium citrate at 30% as anticoagulant. Samples were then centrifuged and kept frozen at −20°C until zinc level determination. Blood samples for ZPP, hematological, and biochemical parameters were obtained in the same day using different tubes.

An intramuscular injection of 100 mg iron (Ferric Polymaltose Complex, Altana Pharma Ltda, São Paulo, Brazil) was given every 15 days. Each patient was given 3 injections. No side effects were observed with iron injections. The hematological and biochemical parameters were obtained before the treatment and 2 weeks after the third injection.

Laboratory Determinations

Hematological and biochemical variables were measured using standard techniques. Plasma and erythrocytes zinc measurements were performed in an atomic absorption spectrophotometer (Hitachi Z 5000; Hitachi Instruments Inc, San Jose, CA) at the standard wavelength of 213.9 nm. A linear standard curve resulted, and a correlation coefficient (r) of 0.999 was calculated from it. Normal zinc concentrations are values higher than 70 μg/dL in plasma and between 40 and 44 μg Zn/gHb in erythrocytes.[14]

ZPP measurement was performed by an hematofluorometer (Helena, Beaumont, USA). In healthy subjects, a ZPP concentration lower than 40 μmol/mol heme is considered normal.[7]

Ferritin was measured using a chemiluminescence immunoassay method (normal values >100 μg/L),[15] and plasma iron level was determined using the iron ferrozine assay, based on the guanidine hydrochloride/ferrozine reaction (normal range, 60 to 140 μg/dL). Transferrin saturation was calculated as plasma iron ÷ total iron binding capacity × 100. Iron deficiency was considered absolute in CKD patients when plasma ferritin concentration was lower than 100 μg/L and transferrin saturation was lower than 20%.[16]

The degree of acidosis was assessed by venous bicarbonate concentration, using a specific electrode (normal value range = 24 to 28 mEq/L).[17]

Diet Analysis

Each patient was instructed on how to fill in a 24-hour food record. Based on the reported food

Table 1. Demographic, Clinical, and Biochemical Characteristics of the Patients

Characteristic	Value
N	38
Gender (M/F)	24/14
Age (y)	54.7 ± 16.1
Creatinine clearance (mL/min/1.73 m^2)	34.5 ± 13.3
Plasma creatinine (mg/dL)	2.7 ± 1.1
Plasma bicarbonate (mEq/L)	24.9 ± 3.6
PNA (g/kg/day)	0.96 ± 0.26
BMI	25.3 ± 4.5
Etiology of CKD	HA = 26, PKD = 3, CG = 4, other = 6

Abbreviations: PNA, protein equivalent of nitrogen appearance; BMI, body mass index; HA, hypertension; PKD, polycystic kidney disease; CG, chronic glomerulonephritis.

record, each patient meal was then prepared in the Laboratory of Experimental Nutrition, mixed and homogenized in a household blender. The diets were then freeze-dried and again mixed and homogenized. For analytical purposes each sample was divided into 2 portions. One of the portions was kept at the laboratory for macronutrient analysis, and the other was sent to the Neutron Activation Laboratory of IPEN/CNEN-SP for iron and zinc level determinations.

The nutrient analysis included: (1) moisture (losses at 105°C), (2) protein (Micro Kjeldahl method), (3) lipids (Soxhlet method), (4) ash (fixed mineral residue), and (5) Nifext fraction methodology (Association of Official Analytical Chemists).[18]

Instrumental Neutron Activation Analysis was used to determine iron and zinc concentrations in the diets of the patients. Iron and zinc synthetic standards were prepared from SPEX CERTPREP standard solutions. The synthetic standard preparation has been previously described.[19] The reference materials Typical Diet (SRM NIST 1548[a] and Orchard Leaves (SRM NIST 1541) were used for checking the precision and accuracy of the method. The within-patients coefficient of variation of the analysis of nutrients in the homogenized diets was <4%.

Statistical Analysis

Results are expressed as mean±SD. The paired Student *t* test was used to compare patient data before and after iron supplementation. The Spearman rank correlation coefficient was calculated to test quantitative association between the parameters. Categorical variables were analyzed by the χ^2 test or the Fisher exact test when indicated. Significant differences were considered when $P < .05$. Calculations were performed using SPSS for Windows (8.0, 1998, SPSS Inc, Chicago, IL).

Results

The main demographic, clinical, and biochemical characteristics of the patients are shown in Table 1. Age varied between 18 and 70 years, and creatinine clearance between 14.0 to 62.0 mL/min/1.73 m^2. Protein equivalent of nitrogen appearance was lower than 0.6 g/kg/day in 10.5% of the patients and higher than 1.0 g/kg/day in 31.5% of them. Body mass index ranged from 20.5 to 41.6.

The effect of iron supplementation on iron and zinc parameters is shown in Table 2. There were no changes in hemoglobin and plasma iron concentrations after iron supplementation. However, transferrin saturation and plasma ferritin increased significantly, associated with a decrease in total iron binding capacity. Before supplementation, transferrin saturation was below 20% in 55% of

Table 2. Effects of Iron Supplementation on Iron and Zinc Status of the Patients

	Before	After	*P* value
Hemoglobin (g/dL)	11.7 ± 1.6	11.9 ± 1.4	.3
Plasma iron (μg/dL)	65.1 ± 24.5	73.0 ± 21.3	.2
Total iron binding capacity (μg/dL)	337.3 ± 45.0	317.5 ± 43.8	<.05
TFS (%)	19.5 ± 7.4	23.2 ± 6.7	<.05
Ferritin (ng/mL)	86.3 ± 67.5	105.4 ± 63.7	.002
Plasma zinc (μg/dL)	76.4 ± 16.7	73.5 ± 10.4	.1
Erythrocytes zinc (μg/gHb)	49.0 ± 7.6	45.5 ± 7.3	.001
ZPP (μmol/mol heme)	64.2 ± 29.2	61.27 ± 23.6	.16

Abbreviations: TFS, transferrin saturation; ZPP, zinc protoporphyrin.

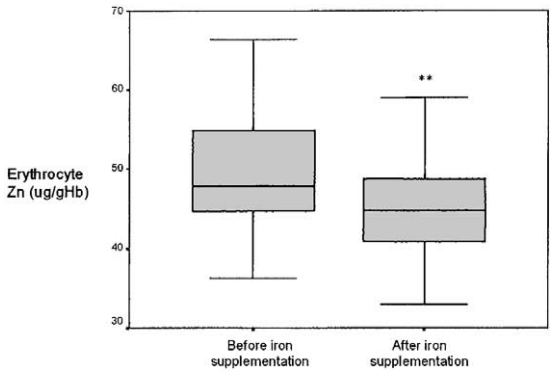

Figure 1. Erythrocyte zinc concentrations before and after iron supplementation.

the patients, and this frequency decreased to 32% of the patients after the iron supplementation ($P = .06$). Plasma ferritin concentration increased in 73% of the patients after iron supplementation. Nevertheless, these values increased to above 100 ng/mL in only in 3 patients. Considering the 2 previous indices, absolute iron deficiency (transferrin saturation <20% and ferritin <100 ng/mL) was present in 41% of the patients and decreased to 15.7% of them after iron supplementation ($P = .004$). Mean plasma zinc concentration was within the normal range and did not change significantly after iron supplementation. However, although in the borderline of significance, the frequency of patients with plasma zinc levels lower than 70 μg/dL decreased from 46.1% to 23.7% ($P = .08$). At baseline, plasma zinc was 76.4±16.7 μg/dL and after iron treatment was 73.5±10.4 μg/dL ($P = .1$).

On the other hand, mean erythrocyte zinc concentration was elevated (49.0±7.6 μg Zn/gHb) and decreased significantly after supplementation (45.5±7.3 μg Zn/gHb) (Table 2 and Fig 1). The decrease in erythrocyte zinc level was observed in 33 of 38 patients. Before iron supplementation, 76.3% of the patients had erythrocyte zinc levels higher than 44.0 μg Zn/gHb; this frequency decreased to 50.0% after the iron supplement ($P = .03$).

ZPP concentration did not change significantly after iron supplementation (Table 2). Before supplementation, 87.0% of the patients had a ZPP concentration higher than 40 μmol/mol heme, and in 4 patients (13.0%) ZPP was higher than 90 μmol/mol heme (126±28.2 μmol/mol heme). After iron supplementation the ZPP concentration of these 4 patients decreased to 99.8±30.2 μmol/mol heme.

The analysis of the diet showed energy and protein intakes of 26.2±7.1 kcal/kg/day and 0.89±0.2 g/kg/day, respectively. Iron intakes were 6.0±2.0 mg/day for the female and 6.3±2.8 mg/day for the male subjects, whereas zinc intakes resulted 5.2±1.2 mg/day for the female and 6.6±2.6 mg/day for the male subjects.

Considering the data before iron supplementation, positive correlations between plasma zinc levels and transferrin saturation ($r = 0.40$, $P = .005$) and plasma zinc and plasma iron levels ($r = 0.41$, $P = .004$) were observed. A weak but significant inverse correlation was found between plasma iron and erythrocyte zinc levels ($r = -0.24$, $P = .05$) and between ferritin and ZPP levels ($r = -0.27$, $P = .001$). After iron supplementation an inverse correlation was also found between plasma zinc and erythrocyte zinc levels ($r = -0.38$, $P = .01$). The correlation between these 2 zinc parameters was even stronger when patients with absolute iron deficiency were analyzed separately (n = 14, $r = -0.72$, $P = .004$).

There were significant correlations between protein intake and zinc intake ($r = 0.74$, $P = .0001$) and iron intake ($r = 0.52$, $P = .01$). No significant correlations were observed between nutrient intake and biochemical parameters.

Discussion

In our early report,[4] we observed that absolute iron deficiency occurs on nondialyzed patients, and that there is an abnormal distribution of zinc in these patients. In this study we tested the hypothesis that iron supplementation and thus the correction of iron deficiency could reduce the abnormally elevated erythrocyte zinc concentration frequently observed in CKD patients.[2-4]

This hypothesis was based on the fact that in situations of iron deficiency, zinc instead of iron is incorporated into the protoporphyrin IX ring of heme, leading to an increase in the concentration of red blood cell ZPP. In fact, many studies have shown an inverse association between parameters of iron status and ZPP.[9-11] The increase in ZPP concentration in red blood cells during iron deficiency could explain at least in part the elevated zinc concentration in erythrocytes in CKD patients.[7,9]

In the present study, we found a high prevalence of iron deficiency considering either transferrin saturation or ferritin concentration. Moreover, absolute iron deficiency was present in 41% of the patients. This condition was also observed by other investigators in nondialyzed CKD patients.[5,6,20] The causes of iron deficiency in this population are multiple, but low iron intake plays an important role.[5,21] Comparing the iron intake of our patients with the new recommended values set by the Food and Nutrition Board for healthy individuals[22] (8 mg iron/day for men from 19 to 70 years old and for women from 51 to 70 years old, and 18 mg iron/day for women from 19 to 50 years old), it is clear that the diet was quite deficient in iron. The reduced iron intake may be a consequence of both low food intake caused by anorexia and the low-protein diet prescribed for these patients. In fact, a direct correlation between protein and iron intake was found in our study.

After 3 injections of intramuscular iron, an improvement in the majority of the iron status parameters such as ferritin and transferrin saturation was observed. Nevertheless, the correction of iron deficiency was not complete, because iron parameters remained inadequate in a significant number of patients. Possibly a longer treatment period, higher dosages, and another route of iron supplementation would have been necessary to completely correct iron deficiency.

Before iron supplementation, the zinc status of our patients was very similar to what has been found by our group and other investigators.[4,23–27] That means a normal to low concentration of zinc in plasma but high in the erythrocytes. The causes for this abnormal distribution are poorly understood. This condition makes the assessment of zinc status of these patients quite difficult because it is not possible to be sure whether this represents a true zinc deficiency.

Aside from the expected changes in the iron parameters, the use of 300 mg intramuscular iron also caused a significant decrease in the erythrocyte zinc level, and the plasma zinc level was correlated inversely with the erythrocyte zinc level, in the population as a whole, and in a more relevant manner in those patients with absolute iron deficiency. This result suggests a possible shift between plasma and erythrocyte zinc levels.

In contrast with other studies, our results have not shown the effectiveness of iron treatment in decreasing ZPP concentration.[10,11,28] Possibly, the incomplete correction of iron deficiency because of the short period of treatment could explain this result.

Canavese et al[28] showed that in hemodialyzed patients ZPP levels decreased only after 1 year of treatment with intravenous iron (0.5 to 1 mg/kg/week). Moreover, the response of ZPP to iron treatment seems to be more effective when its concentration is higher than 90 μmol/mol heme, which characterizes absolute or functional iron deficiency. Accordingly, treatment with 100 mg intravenous iron over 10 injections in hemodialyzed patients reduced ZPP only in patients with ZPP concentrations above this value.[10] Braun et al[11] also showed no significant change in ZPP levels after iron supplementation (24 doses of 40 mg of intravenous iron) in patients with ZPP levels lower than 90 μmol/mol heme. In this study only 4 patients presented ZPP levels higher than 90 μmol/mol heme, and in all of them the concentration of ZPP decreased after the treatment with iron.

Our results suggest that the mechanisms involved in the maintenance of elevated erythrocyte zinc in CKD patients seem not to be related only to ZPP because erythrocyte zinc concentration decreased even in the absence of ZPP reduction after iron supplementation. Thus, it is clear that there is a link between iron and zinc metabolism in these patients. This raises the possibility that other mechanisms are involved with this relationship. One of them could be related to the red-cell concentration of carbonic anhydrase (CA) because the active sites of all CA classes function with a single zinc atom that is essential for catalysis. In iron deficiency anemia, the increased CA levels are believed to be a compensatory mechanism in which hemoglobin can act as a proton acceptor from the active site of carbonic anhydrase during the hydration of CO_2 (and vice versa). The increase of carbonic anhydrase can facilitate, via the Bohr effect, the transfer of the oxygen to the peripheral tissues. Therefore, an increase in red-cell CA can constitute a compensating mechanism to anemic hypoxia in uremic patients.[29]

A recent study showed that CA levels did not change after iron supplementation, and it was concluded that the CA erythrocyte concentration in CKD patients is increased, but this cannot be explained by iron deficiency or acidosis.[30]

Another hypothesis for explaining the elevated zinc erythrocyte levels in these patients could be the concentration of antioxidant enzymes. Some studies show that zinc superoxide dismutase in erythrocytes of nondialyzed patients is significantly elevated.[31,32] However, to our knowledge, these hypotheses have not yet been tested.

In conclusion, the results of this study raise the possibility of an association between iron deficiency and derangements of zinc metabolism. Iron supplementation in CKD and the correction of iron deficiency could decrease erythrocyte zinc levels. However, large clinical studies are necessary to consolidate the causes of abnormalities of zinc in uremia.

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