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# Co-Existence of Iron Deficiency and Zinc Deficiency in Patients with Microcytic Hypochromic Anemia

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## Abstract

**Background:** Zinc (Zn) and iron (Fe) are essential micronutrients for human body and these are involved in many complex enzyme systems. Nutritional anemia is among the ten major causes for hospital admission in Sudan. However, nationally representative data on iron deficiency are limited in the country. There is no published data regarding co-existence of iron deficiency and zinc deficiency among Sudanese population.

**Objective:** To measure the serum Zn level among Sudanese patients presenting with iron deficiency anemia (IDA) to determine the status of Zn deficiency anemia (ZDA) and its positive impact on patients' health.

**Materials and methods**: An analytical cross-sectional study was carried out at Ibrahim Malik Teaching Hospital (Khartoum State, Sudan), in November 2019. A total of 68 patients with IDA were enrolled in the study. Laboratory and patients data were analyzed using the Statistical Program for Social Sciences (SPSS).

**Results:** Serum Zn level was found within normal range in 2.9% (2/68) of IDA patients, while 97.1% (66/68) of IDA patients were found to have zinc deficiency. No significant difference was observed between zinc deficiency, serum ferritin level, and gender ($p = 0.79$ and $p = 0.17$ respectively). A significant difference was observed between hemoglobin level and gender ($p = 0.03$). Also, a statistically significant difference was observed between age incidence and zinc deficiency ($p = 0.036$) and hemoglobin level ($p = 0.018$). No significant difference was observed between age incidence and serum ferritin level ($p = 0.6$). Zinc deficiency level was found lower in IDA patients with 2-5 ng/ml serum ferritin level, than in IDA patients with 6-9 ng/ml without a statistical difference ($p = 0.49$). Also, no statistical difference was observed between MCV level, hemoglobin level, and zinc deficiency ($p = 0.35$ and $p = 0.63$ respectively). Zinc deficiency level was found lower in IDA patients with a 15-22 g/dl MCHC level as compared with those with MCHC 23-30g/dl level. Zinc deficiency was found lower in IDA patients (with 12-18 pg Hb) and in IDA patients (with MCH level lower than 19-24pg). No a statistical difference ($p = 0.19$) was observed between the lower level of zinc deficiency observed in IDA patients with 12-18pg MCH level as compared with those with 19—24 pg MCH level ($p = 0.40$).

**Conclusion:** Zinc deficiency and low serum ferritin levels were observed among Sudanese patients with iron deficiency anemia. Women and children were found to be more prone to hemoglobin and zinc deficiencies. Iron + zinc combination might be more effective for treatment of iron deficiency anaemia.

**Keyword**: Ion deficiency anemia, Zinc deficiency anemia, Microcytic hypochromic anaemia.

## Introduction

Anemia affects low, middle and high income population and causes both mortality and disability worldwide. The World Health Organization estimates that 2 billion people (over 30% of the world's population) are anemic. Approximately 50% of cases of anemia are considered to be due to iron deficiency and the highest proportion of individuals affected are in Africa[1].

Anemia affects 47.4% of children under the age of 5 years, 25.4% of school age children, 30.2% of non-pregnant women, 41.8% of pregnant women, 12.7% of me, and 23.9% of the elderly[2].

The deficiency of micronutrients is a health issue far from being resolved globally. Some mineral deficiencies such as iron and zinc impact negatively on physical growth, immune response, cognitive and emotional development, among others[3].

Nutritional anemia is among the ten major causes for hospital admission in Sudan. However, nationally representative data on iron deficiency are limited in Sudan. In Khartoum the prevalence rate was the lowest and affect almost one third of children. In 2004, and during the crisis that affected Darfur population, the prevalence rate of anemia was 55%. Severe anemia affected more than 1% of children[4].

Iron deficiency (ID) may be prevalent in a total of 25% of the world's population. Infants, young children, females, adolescents, and pregnant and lactating mothers are the most affected by ID in developing countries[5] .

Anemia may be acquired either by disorders or deficiencies of micronutrients such as folic acid, vitamin B12 and iron. Although recent survey data are lacking, there is a clear evidence that micronutrient deficiencies such as vitamin A, iodine, and iron are a major public health problem in Sudan. Approximately half of the cases of anemia are due to iron (Fe) deficiency, which may be the result of an increased loss of iron from the body or an inadequate intake or uptake of this trace element[6].

IDA can be caused by diets with low bioavailability of iron. The limited consumption of meat is probably a major cause of anemia. Parasitic diseases are very common and are also an important cause of IDA. Schistosomiasis is one of the main endemic water-borne diseases in Sudan[4].

Symptoms among Zn and Fe deficiency cases are abundant and they can show similarities. Most important co existence of deficiency of these two trace elements aggravate the symptoms of anaemia[5].

Zinc (Zn) is an essential nutrient for all forms of life and many body functions are linked to zinc containing enzymes[7].

The human body contains 2-3g of zinc, and nearly 90% of zinc is found in muscles and bone. Other organs containing estimable concentrations of zinc include the prostate, liver, the gastrointestinal tract, kidney, skin, lungs, brain, heart, and pancreas[8].

Zinc deficiency affects many organ systems, including the integumentary system, the gastrointestinal system, the central nervous system, the immune system, the skeletal system, and

The reproductive system. Zinc deficiency results in dysfunction of both humoral and cell-mediated immunity and increases the susceptibility to infection. Disturbances in nucleic acid metabolism and protein synthesis may account for some features of zinc deficiency[7].
The present study aims to measure the serum Zn level in Sudanese patients presenting with iron deficiency anemia in order to determine the co-existence of Zn deficiency and to assess whether this will have a positive impact on patients' health.

## Materials and Methods

This descriptive cross sectional study was carried out in Khartoum State in November 2019. The study aimed to determine the co-existence of iron deficiency and zinc deficiency in patients with microcytic hypochromic anemia.
A total of 70 patients with IDA were investigated at Ibrahim Malik Teaching Hospital (Khartoum, Sudan).
Blood samples and data collection: Venous blood samples were collected in EDTA and plain tubes. The plain containers blood samples were centrifuged (within 1 hr after collection to separate the serum which was transferred to screw-cap tubes for zinc and ferritin estimation, using the enzyme-linked immunosorbent assay technique (Human Reader HS Human and Diruics-T240 auto-chemistry analyzer respectively).
EDTA samples were analyzed by the automated hematology analyzer (Mindry BS-300) to estimate hemoglobin level and red cell indices.
Inclusion criteria: Patients with microcytic hypochromic anemia and low serum ferritin level.
Exclusion criteria: Patients complaining of other types of anemia, patients receiving iron therapy, and patients with medical conditions known to cause iron deficiency anemia.
Data analysis: Data were analyzed using the Statistical Program for Social Sciences, version 20. Data were double-checked before analysis. Cross tabulation was used to evaluate the association between variables and p-value $< 0.05$ was considered significant.
Ethical approval: The study received ethical clearance from the Ethical Board of Al Neelain University (Khartoum). Verbal consent was taken from all patients investigated.

## Results

A total of 68 Sudanese patients with IDA were enrolled in this study. All participants were suffering from zinc deficiency (normal range of zinc: males 72.6-127 ug/dl, females: 70.6-114 ug/dl, and children: 63.8-110 ug/ml) and ferritin deficiency (normal range of ferritin: males: 10-220 ug/dl and females 10-124 ug/dl).
Lowest ferritin level among males was 51.5% (35/68) and among females was 48.5% (33/68) in different age ranges and ethnicity.
There were 20 cases (29.4%) within the 0-15 age range and 27 cases (39.7%) within the 16-30 age range, and 21(30.9%) cases within the 31-45 age range.
As shown in Tables 1, 2, 3, 4, and among these IDA patients, no significant difference was observed between zinc deficiency and serum ferritin level and gender ($p = 0.50$; and $p = 0.86$ respectively), while a significant difference was observed between hemoglobin level and gender ($p = 0.016$).
There was no significant difference between serum ferritin level and gender incidence ($p = 0.23$).

Table 1: Association between zinc deficiency (ug/ml) and ferritin level (ng/ml)

| Parameter | | Ferritin | | Total |
|---|---|---|---|---|
| | | 2-5 | 6-9 | |
| Zinc | 25-45 | 17(34.6%) | 05 (26.3%) | 22 |
| | 46- 65 | 32(65.4%) | 14 (73.7%) | 46 |
| Total | | 49 | 19 | 68 |

Table 2: Association between zinc deficiency (ug/ml) and gender

| Parameter | | Gender | | Total |
|---|---|---|---|---|
| | | Male | Female | |
| Zinc | 25-45 | 11 (31.4%) | 11 (33.4%) | 22 |
| | 46-65 | 24 (68.6%) | 22 (66.6%) | 46 |
| Total | | 35 | 33 | 68 |

Table 3: Association between hemoglobin (g/dl) and gender

| Parameter | Gender | | Total |
|---|---|---|---|
| | Male | Female | |
| 6-10 g/l Hb | 11 (31.4%) | 20 (60.6%) | 31 |
| 2-5 g/l | 24 (68.6%) | 13 (39.4%) | 37 |
| Total | 35 | 33 | 68 |

Table 4: Association between serum Ferritin level (ng/ml) and gender

| Parameter | | Gender | | Total |
|---|---|---|---|---|
| | | Male | Female | |
| Ferritin | 2-5 | 23 (65.7%) | 26 (78.8%) | 49 |
| | 6-9 | 12 (34.3%) | 07 (21.2%) | 19 |
| Total | | 35 | 33 | 68 |

Also, as shown in Tables 5, 6, 7), a statistically a significant difference was observed between the age incidence and zinc deficiency (p = 0.032), and hemoglobin level (p = 0.013). No significant difference was observed between age incidence and serum ferritin level ((p = 0.5).

Table 5: Association between zinc deficiency (ug/ml) and age incidence (years)

| Parameter | | Age | | | Total |
|---|---|---|---|---|---|
| | | 0--15 | 16--30 | 31—45 | |
| Zinc | 25—45 | 11 (55.0%) | 07 (25.9%) | 04 (19.0%) | 22 |
| | 46—65 | 9 (45.0%) | 20 (74.1%) | 17 (81.0%) | 46 |
| Total | | 20 | 27 | 21 | 68 |

Table 6: Association between hemoglobin (g/dl) and age incidence (years)

| Parameter | | Age | | | Total |
|---|---|---|---|---|---|
| | | 0--15 | 16—30 | 31—45 | |
| Hb | 6--10 | 12 (60.0%) | 15 (55.6%) | 04 (19.0%) | 31 |
| | 2—5 | 08 (40.0%) | 12 (44.4%) | 17 (81.0%) | 37 |
| Total | | 20 | 27 | 21 | 68 |

Table 7: Association between ferritin level (ng/ml) and age distribution (years)

| Parameter | | Age | | | Total |
|---|---|---|---|---|---|
| | | 0-15 | 16-30 | 31-45 | |
| Ferritin | 2-5 | 14 (70.0%) | 18 (66.7%) | 17 (81.0%) | 49 |
| | 6-9 | 06 (30.0%) | 09 (33.3%) | 04 (19.0%) | 19 |
| Total | | 20 | 27 | 21 | 68 |

## Discussion

Zinc is an essential trace mineral whose abundance among transition metal ions in all living organisms is second only to that of iron[9].

It functions as a cofactor or structural stabilizer for more than 300 enzymes throughout the body and directs a wide array of biochemical and cellular processes, including signal transduction, ribonucleic acid (RNA) transcription, and cellular growth, division, and differentiation[10, 11].

Interestingly, patients with IDA have been shown to have significantly reduced serum levels of zinc while IDA is significantly more prevalent in patients known to have zinc deficiency[11, 12].

More specifically, zinc deficiency has been speculated to contribute to the development of IDA through the inhibition of the intestinal absorption of iron as well as its mobilization from tissue stores[13].

Iron deficiency anemia often shows association with low serum zinc levels, in infancy and young children. These changes in zinc status are frequently explained by coexisting deficiencies of iron and zinc due to the common dietary sources of both micronutrients and decreasing their intestinal absorption by the same dietary factors[5].

Zinc deficiency was reported to occur along with the iron deficiency in the studies on the ID and IDA as well as trace element deficiency. The International Zinc Nutrition Consultative Group concluded that breast milk is a sufficient source of zinc for normal birth weight term infants until approximately 6 months of age[14].

This is a descriptive cross-sectional study, presented evidence for a high prevalence of hemoglobin, zinc, Ferritin. MCV, MCH and MCHC deficiencies in Sudanese male and female children and adults suffering from IDA. Females and children were more prone to suffer most of hemoglobin deficiencies. In the present study, the levels of serum zinc in these patients with IDA were lower in comparison to reference levels; many studies reported the co-existence of iron deficiency and zinc deficiency in patients with microcytic hypochromic anemia. A study done by Karasu *et al*, in which they reported that a statistically significant correlation in a positive way was observed between zinc value and age, hemoglobin, hematocrit, MCV, Fe, ferritin, TSI[5], which is parallel to the present study in which, zinc deficiency was found in IDA patients with low serum ferritin level, low Hb level and low MCV, MCH, MCHC level, with no significant difference was observed between zinc deficiency, serum ferritin level and gender and significant difference was observed between zinc deficiency and hemoglobin level and gender. In a study done by Guansheng, revealed that deficiency of iron and zinc is of significance for public health in China. Children, women and older people in both urban and rural areas are the vulnerable

groups for iron deficiency[6].

This study is agreed with the current study which reported children and women were most susceptible to zinc and iron deficiency and agreed with a study done by Mohamed *et al*, in which they found that the Sudanese patients have very low concentrations of zinc compared to a control group of healthy individuals, while all Dutch patients had normal zinc levels. When matched for haemoglobin level, they still showed lower zinc concentrations. Even in the Sudanese patients without a known history of malnutrition and in patients with the anemia of chronic disease zinc levels were significantly lower than in the controls[2], and agreed with a study done by Ece *et al*, in which they reported that zinc deficiency was observed along with IDA in children in the 1-14 age group[13].

Iron deficiency is the most common nutritional deficiency in both developing and developed countries[15].

Iron deficiency anemia can co-exist with deficiencies of other trace elements such as zinc, which is more frequently encountered in developing countries. Zinc is found in the structure of metalloproteins and more than 300 types of enzymes. Zinc functions as the catalyst in iron metabolism in the activity of alpha-aminolevulinic acid dehydratase enzyme, which has a role in heme synthesis[16].

The dietary source of zinc is mainly meat and chicken, but it is also found in nuts and lentils. Mild zinc deficiency appears to be common, especially in developing countries. Individuals in developing countries are at risk of zinc deficiency because the diet is relatively low in zinc and contains significant amounts of phytates, which reduce zinc absorption. Zinc is absorbed mainly in the duodenum and jejunum and to a lesser extent in the ileum and large intestine. It shares some common absorptive components with iron and copper, and the three minerals may compete for absorption[17].

Another cause of low serum zinc concentrations in IDA may be the incorporation of zinc instead of iron into protoporphyrin in iron deficiency, which then results in increased production of zinc protoporphyrin instead of heme. In addition, the cause of a positive correlation between serum zinc and MCV levels in subjects with IDA may be over-production of zinc protoporphyrin in smaller erythrocytes (severe iron deficiency).Thus, in severe iron deficiency, erythrocytes may contain more zinc protoporphyrin, and as a result of the excessive utilization of zinc, serum zinc concentrations may below[18].

It has been long known that zinc deficiency is associated with abnormalities in iron metabolism and iron deficiency anemia. However, studies in literature have usually been conducted on a pediatric age group[18]. Gurgoza *et al*. found that zinc levels were low in adult IDA patients[19].

In another study, Upadhyaya *et al*. screened 80 pregnant women and found that serum zinc levels were decreased in 34 women diagnosed with IDA[20].

In the current study, low serum zinc levels were investigated in IDA. Iron and zinc metabolisms have some common pathways, and thus, these two elements affect each other. Although some hypotheses have been suggested in clinical trials, sufficient knowledge has not so far been acquired to explain these mechanisms. In iron deficiency, the production of zinc protoporphyrin is increased for heme production and serum zinc level is decreased because of zinc consumption[21].

King et al. suggested that in zinc deficiency, bone marrow erythroid precursors are decreased and the erythropoietin level is also decreased[22].

Thus, the results of the current study support these findings with the demonstration of decreased serum zinc levels in iron deficient patients. Iron deficiency anemia can be associated with irritability, palpitations, dizziness, breathlessness, headache, and fatigue. Fatigue is a particularly common complaint among patients[23].

In the current study, all the patients with IDA had complaints of fatigue (100%).Patients with long-standing iron deficiency may develop a constellation of symptoms characterized by defective structure or function of epithelial tissues. Especially, the nails, the tongue and mouth, the hypopharynx, and the stomach are affected[23].

In the current study, epithelial manifestations were seen in 53.5 % patients with IDA and 88 % of patients with IDA and zinc deficiency. There was a statistically significant difference between zinc deficient IDA patients and patients with normal serum zinc level. Zinc deficiency is known to cause epithelial barrier dysfunction in the gastrointestinal tract[24, 25] (diarrhea and glossitis) and skin (alopecia and dermatitis)[25, 26] and also causes nail dystrophy[15].Together with IDA, it aggravates the epithelial barrier dysfunction in the skin and gastrointestinal tract[25].

**Conclusion:** Among these patients with IDA, the present study concludes the levels of serum zinc and serum Ferritin in these patients with IDA was lower in comparison to reference levels. Females and children were more prone to suffer most of hemoglobin deficiencies, significant differences were observed between zinc deficiency and hemoglobin level, gender and age distribution, while no significant difference was observed between zinc deficiency and serum ferritin level.

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