Original article

Serum zinc level in Iron Deficiency and Iron Deficiency Anemia of children aged 6 months to 5 years

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Summary. *Background:* Iron Deficiency Anemia (IDA) is the most common anemia in all age groups. The coexistence of iron deficiency anemia and zinc (Zn) deficiency is quite common, for most of the etiologic factors are common. The purpose of this study is to determine the prevalence of zinc deficiency in children with iron deficiency and/or iron deficiency anemia. *Method:* One hundred and sixty child patients within 6month-5 year age range diagnosed with iron deficiency and/or iron deficiency anemia and 91 children with no iron deficiency and/or iron deficiency anemia diagnosis were included in the study. The relationships between serum zinc levels and other biochemical and hematological parameters were examined. *Results:* It was observed that the study and control groups had similar demographic characteristics, and there was no statistically significant difference between two groups in terms of average age (months), distribution of age groups, and gender groups. Statistically significant differences were observed between hemoglobin (Hb), haematocrit (Hct), mean corpuscular volume (MCV), red cell distributionwidth (RDW), iron (Fe), total iron binding capacity (TIBC), transferrin saturation (TS) and Ferritin values of the study group and control group, and the cases in the study group were determined to be highly anemic. Statistically significant difference was determined between groups in terms of zinc levels, and zinc levels in the study group were determined to be lower than those in the control group. Zinc deficiency (10%) in children diagnosed with iron deficiency and/or iron deficiency anemia was found more common compared to the control group (2.2%). A positive correlation between serum zinc levels and Hb, Hct, MCV, Fe, TS and Ferritin, and a negative correlation between serum zinc levels and RDW and total TIBC were detected in the study group. *Conclusion:* According to these results, it was concluded that children with iron deficiency could simultaneously have zinc deficiency, the iron-zinc combination might be more effective for the treatment of iron deficiency than treatment with only iron, and early age supplementation programs might be useful for the highrisk groups such as childhood until zinc deficiency tests gave routine results.

Key words: iron deficiency anemia, zinc deficiency, children

Introduction

Zinc (Zn) and iron (Fe) are essential micronutrients for human body and these are involved many complex enzyme systems (1). Children with Iron Deficiency Anemia (IDA) have low serum Zn levels. Inadequate intake of Zn is considered to be responsible for 20 % of global child mortality (2). Zinc and Fe affects the absorption of each other level in intestinal mucosa. Phytate and excessive intake of mineral supplements may be impair Zn and Fe absorption (3). Deficiency of trace element nutrients is seen common in children. Because of the increased requirements, inadequate intake, and recurrent infections, in developing countries especially infant and young children are vulnerable to Zn and Fe deficiency (4). Zinc is an important, trace elements that affects catalytic, structural and regulatory functions in human body. Iron is important for synthesis of hemoglobin and myoglobin (5). Iron deficiency (ID) can be seen a total of 25% of the world's population. Infants, young children, females, adolescents and pregnant and lactating mothers are most affected by ID in developing countries (6-8). Only 35–55% of cases of IDA in children are solely due to iron deficiency and others are associated with changes in status of multiple trace elements. ID and IDA are more common in Turkey than developed countries. Previous studies had reported that ID rate between 1.5% to 62.5% in pediatric age group in Turkey (9-11). Nutritional zinc deficiency is also quite common in the world and in Turkey at rates as high as 15.7% (12,13). Although Fe and Zn deficiency had been reported different region of world, frequency rate can be various by country (14-16). Deficiency of zinc, is frequently associated with IDA in developing countries and in Turkey (2).

Symptoms in Zn and Fe deficiency cases are abundant and they can show similarities. Most importantly co existence of deficiency of these two trace elements aggravate the symptomps.

Most of the researchers have shown lower serum zinc levels in patients with iron deficiency anemia in comparison to nonanaemic patients (2, 17, 18), but others have not found significant differences in serum zinc between iron deficiency anemia patients and healthy controls (19-21). Studies are limited related with iron deficiency anemia and micronutrient deficiency in children.

In this present study, we aimed to measure serum Zn level in children between the ages of 6 months and 5 years with Fe deficiency or Fe deficiency anemia in order to determine if Zn deficiency accompanies it.

Materials and Method

The study was conducted by Bagcilar Training and Research Hospital Pediatrics Outpatient Clinic, Istanbul, Turkey November 2014 and July 2015. One hundred sixty patients whose ages were between 6 months and 5 years and who had ID and/or IDA were included in the study. Within the control group, zinc level in the serum samples obtained from 91 healthy children who had no iron deficiency and iron deficiency anemia presented in the same period was studied.

Patients with findings supporting the absorption and bleeding disorder in the gastrointestinal system and patients with findings supporting a chronic disease and thalassemia or other hemoglobinopathies were excluded from the study. The study approved by Bagcilar Training and Research Hospital Board Ethics Committee. The complaints of the patients were recorded; their physical examination was performed after measuring their weight and height.

After obtaining the informed consent, 2cc of venous blood were taken into the standard purple cap CBC tube containing 0.072 ml 7.5% K3-ethylenediaminetetraacetic acid for a complete blood count; 4cc of blood were taken into the yellow cap biochemistry tube not containing anticoagulant in order for Fe, TIBC, ferritin and zinc levels were to be studied.The peripheral blood smear stained with Wright's stain was examined by a light microscope. For full blood count, automatic hemocytometer Roche XT 1802 daily calibration of which was performed daily was used. Fe and total iron binding capacity (TIBC) were studied with Cobos C602 device.

The serum samples were used by dissolving, which were separated from the full-blood at the moment they were received and frozen at -80°C for serum ferritin and zinc values to be studied. The serum ferritin levels were measured by the immune chemiluminescence method using Cobos 6000 device. Full blood cell count, Fe, TIBC, ferritin measurements were performed at the central laboratory of Bagcilar Training and Research Hospital. Zinc levels were studied by the atomic absorption spectrophotometer method (Atomic Absorption Spectrophotometer AA-6701F SHIMADZU, Japan) at a private laboratory.

The transferrin saturation index (TSI) was obtained by proportioning the serum iron to TIBC. Patients with hemoglobin (Hb), hematocrit (Hct) and mean corpuscular volume (MCV) levels under the lower limits according to the age group and with TSI level below 16% and ferritin level below12 ng/dl were considered as IDA. Patients with normal hemoglobin, hematocrit and MCV level according to the age group and having TSI level below 16% and ferritin value below12 ng/dl were considered to be in the iron deficiency group. However, when the ferritin levels of some patients were found high (due to the acute phase reactant of ferritin) although no findings were detected in favor of infection, they were considered to be in the iron deficiency group if TSI was low. Hemoglobin lower limits for age groups were determined based on Dallman anemia criteria. Hemoglobin lower limit was set as 10.5 gr/dl for 0.5-2 age range and as 11.5 gr/dl for 2-6 age range (22). According to this, the cases with higher hemoglobin values than lowerlimits set for age groups, with TSI higher than 16% and with ferritin higher than 12 ng/ml were considered as the control group. Zinc levels were evaluated according to the age groups (Normal values for the age groups; 70-120 μg/dl for 1-5 age range group). Zinc deficiency was defined if <65 μg/dl (23).

Statistical Evaluation

The statistical analysis in this study was performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. Together with the descriptive statistical methods (mean, standard deviation) in the evaluation of the data, an in dependent t-test was used to compare the pairs, the chi-square test was used to compare the qualitative data, and the Pearson correlation test was used in order to determine the relationships of the variables with each other. The linear regression analysis was performed between zinc and other variables. The results were evaluated at p <0.05 significance level and in 95% confidence range.

Results

The study group consisted of 101 male (63.12%), 59 female (36.88%), and the control group consisted of 48 male (52.75%) and 43 female (47.25%) cases. The average age of the study group was 34.86 ± 19.6 months, and the average age of the control group was 39.37 ± 18.96 months. All patients with iron deficiency anemia had a complaint of loss of appetite. In addition to the complaint of loss of appetite, 50 patients (31.25%) were suffering from failure to thrive, 20 patients (12.5%) were suffering from anxiety, 30 patients (18.75%) were suffering from asthenia and getting tired quickly, 10 patients (6.25%) were suffering from pica, 20 patients (12.5%) were suffering from getting ill often, 20 patients (12.5%) were suffering from dizziness and tachycardia, 10 patients (6.25%) were suffering from a headache. All of 16 patients with zinc deficiency were suffering from the loss of appetite and failure to thrive. In addition to these findings, 4 patients had recurrent lower respiratory tract infection, 2 patients had atrichiosis, 4 patients had a decline in school performance, 2 patients had anxiety and 4 patients had recurrent diarrhea history.

The most common physical examination finding was paleness of the skin and mucosa; the other findings were tachycardia, murmur, and a slowdown in growth (Table 1).

Within the study group, there were 81 cases (50.63%) within the 0-2 age range and 79 cases (49.38%) within the 2-5 age range. Within the control group, there were 39 cases (42.96%) within the 0-2 age range and 52 cases (57.14%) within the 2-5 age range. No statistically important difference was observed between the median ages (months) of the study group and control group (p=0.077). No statistically important difference was observed between the age distribution of the study and control groups (p=0.236). No significant difference was observed between the groups in terms of gender (p=0.0108).

The assessment of the study group and control group in terms of zinc, hemoglobin, hematocrit, MCV, RDW, Fe, TIBC, TSI, and ferritin can be seen in Table 2. (Figure 1, 2). Based on these results, the average zinc of the study group was found lower than that of the control group, which was statistically significant (p=0.0001).

Table 1. Examination findings of the patients with anemia, anemia + zinc deficiency

	Paleness of the skin and mucosa	Tachycardia	Murmur	Hair and skin changes	Height 3 percentile	Height 3-10 percentile
Anemia (n)	100	20	10			
Anemia+zinc deficiency (n)	12	2	1	4	5	5

Table2. The Assessment of the Study group and Control Group in terms of zinc, hemoglobin, hematocrit, MCV, RDW, Fe, TIBC, TSI and Ferritin

		Control Group n:91		Study Group n:160		p
Zinc		1.27±0.3		0.94±0.19		**0.0001**
Zinc	< **65** µg/dL	2	2.20%	16	10.00%	**0.021**
	>**65** µg/dL	89	97.80%	144	90.00%	
Hemoglobin		12.69±0.68		10.49±1,07		**0.0001**
Hematocrit		38.35±2.26		33.2±3.11		**0.0001**
MCV		79.63±3.44		70.38±6.4		**0.0001**
RDW		12.19±0.75		14.65±1.98		**0.0001**
Fe		88.52±19.88		34.96±14.22		**0.0001**
TIBC		360.53±77.67		404.3±62.98		**0.0001**
TSI		0.25±0.07		0.08±0.04		**0.0001**
Ferritin		39.33±25.55		22.64±21.55		**0.0001**

Zinc deficiency in the study group was found higher than that of the control group, which was statistically significant (p=0.021). While zinc deficiency of 10% was seen in the study group, this ratio was 2.2% in the control group. The zinc deficiency risk in the study group was found to be 4.94 (1.11-22.02) times higher than that in the control group on average.

A statistically significant correlation in a positive way was observed between zinc value and age, hemoglobin, hematocrit, MCV, Fe, ferritin, TSI. Besides, a statistically significant correlation was observed between zinc and RDW, TIBC in a negative way (Table 3). The linear regression analysis was performedwith hemoglobin, hematocrit, MCV, RDW, Fe, TIBC, TSI and ferritin values among which a significant correlation was observed during the univariate tests, and R= 0.599, R2: 0.359, Corrected R2: 0.336 were found (p= 0.0001).

During the multivariate analysis, Fe (p=0.001) showed a statistically significant relationship (Table 3).

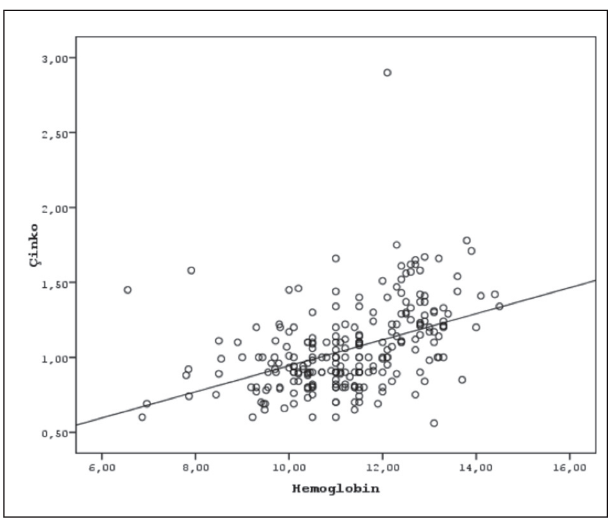

Figure 1. The relationship between zinc and hemoglobin in the study group

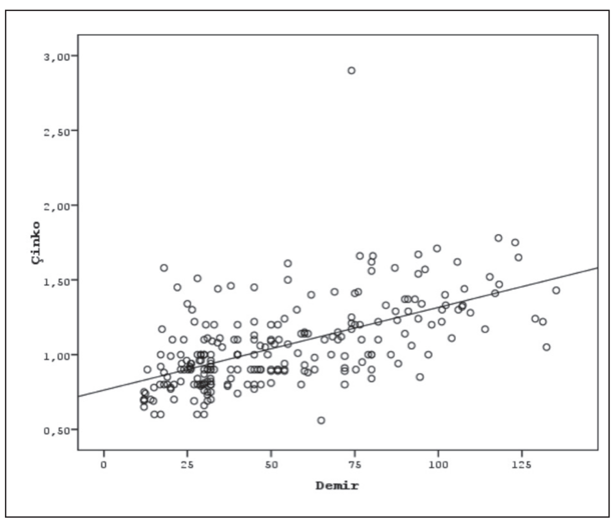

Figure 2. The relationship between zinc and hemoglobin in the study group

Table 3. The correlation between zinc and age, hemoglobin, hematocrit, MCV, RDW, Fe, TIBC, TSI and ferritin values.

		Zinc
Age	r	0.152
	p	0.016
Hemoglobin	r	0.436
	p	0.0001
Hematocrit	r	0.424
	p	0.0001
MCV	r	0.344
	p	0.0001
RDW	r	-0.298
	p	0.0001
Fe	r	0.583
	p	0.0001
TIBC	r	-0.158
	p	0.015
TSI	r	0.580
	p	0.0001
Ferritin	r	0.263
	p	0.001

Discussion

According to the 2001 World health Organization (WHO) report, 30% of the children aged between 0 and 4 years and 48% of the children aged between 5 and 14 years are anemic in developing countries (24). Iron deficiency anemia often shows association with low serum zinc levels, in infancy and young children (2,17).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 (25). 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 (2,5,14,15, 25,26-28). 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. Children start to lose endogenous zinc from non-intestinal sites, such as the urinary tract and skin, after 6 months of age, because infants need more Zn after 6 months of age (29). In children, the highest prevalence of Fe deficiency is found between 4 months and 3 years of age because of the rapid growth and inadequate dietary intake of Fe (26). In the present study, the levels of serum zinc in patients with IDA were lower in comparison to reference levels and controls. The patients in our study were in the 6 month-5 years age range, which is the period of rapid growth. The need of the body for these elements rapidly increases along with the rapid growth. The period following the first6 months is at the same time the transition period to the complementary feeding, and the external intake decreases and, based on this, iron and zinc deficiencies increase within this period.

Duque et al (28) reported in the study they conducted iron and zinc deficiencies constitute the prin-

Table 4. The linear regression results for the multivariate tests.

	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	t	p
Hemoglobin	-0.006	0.032	-0.03	-0.196	0.845
Hematocrit	0.011	0.009	0.141	1.249	0.213
MCV	-0.004	0.004	-0.09	-0.02	0.368
RDW	0.006	0.01	0.045	0.626	0.532
Fe	0.006	0.001	0.576	10.71	**0.001**
TIBC	0.001	0.000	0.029	0.347	0.729
TSI	0.853	0.608	0.273	1.402	0.162
Ferritin	0.001	0.001	0.104	1.762	0.079

cipal micronutrient deficiencies in Mexican children younger than 2 years old and the prevalence of simultaneous iron and zinc deficiencies was 9.2% and 2.7% in urban and rural areas. Ece et al. (2) reported in the study they conducted that zinc deficiency was observed along with IDA in children in the1-14 age group. Additionally, in this study, a positive correlation was identified between serum zinc level and MCV, and no significant correlations were identified among other hematologic parameters and zinc level. In this present study, a statistically significant correlation in a positive way was observed among zinc, hemoglobin, hematocrit, serum iron level, ferritin, and MCV. That a positive relationship of zinc deficiency was identified with these parameters supports the assumption that zinc deficiency occurs along with IDA. In a study carried out in Mexico, iron deficiency prevalence was reported to be 26% and zinc deficiency prevalence was reported to be 13% among children aged 1-4 years (30). In a study carried out in India on children aged 6 months to 5 years, iron deficiency anemia was reported to be 55.8% and zinc deficiency prevalence was reported to be 17.9% (28). It was reported in the study conducted by Özden et al (5) that IDA and zinc deficiency were observed at the same time in the infants in the 6-12 month age range, and these deficiencies were associated with the iron and zinc deficiencies in mothers. The lack of micronutrients in infant period begins with the lack of maternal intake.

Angelova et al (15) reported that trace elements deficiencies including zinc deficiency in the iron deficiency anemia in children under 3 years of age were due to the lack of nutritional intake. A significant correlation in a positive way between age and zinc level was observed in our study. As reported in the literature, zinc deficiency is most commonly seen around 6 months (29). This period is the period of rapid growth in which the need increases and the intake is insufficient. Increased request of zinc due to rapid growth and decreased intake of zinc due to inadequate feeding practices predispose infants and pre-school children, especially living in society of low socioeconomic level, to an elevated risk of zinc deficiency (31). The socioeconomic levels of the patients living in our region are below the average, and it is believed that it is effective in the insufficient intake.

Additionally in this present study, statistical significance in a positive way was also identified between serum zinc level and TSI. Iron and TSI values of the patients, serum zinc levels of whom were low, were lower than those of the patients with higher zinc levels. This finding confirmed the statement that zinc deficiency could be seen in ID without the emergence of anemia. In the study, a negative correlation was observed between RDW and TIBC. RDW and TIBC increases are the expected parameters in iron deficiency anemia, and these are the parameters supporting the statement that zinc deficiency and iron deficiency anemia occur together. In a study carried out on children with IDA aged 6 months to 24 months, a linear correlation was observed between serum zinc level and iron and iron binding capacity (32). Iron deficiency anemia was observed to increase zinc deficiency 5 times. When explaining this correlation, they supported their finding with the opinion that zinc administration to children with IDA decreased the symptoms depending on ID. Furthermore, it was reported that in the co-existence of zinc deficiency and iron deficiency anemia, zinc protoporphyrin increased; when iron decreased in the body, zinc could be used in hemoglobin synthesis instead of iron (33). Park et al. explained the relationship between iron and zinc in their study with this opinion as well. Another mechanism explaining the co-existence of zinc and iron deficiency during infancy is the deficiency in meat intake which is the major source of these two elements. Infants in this age group are fed with grain-based food. Fibre and phytates in grain-based food inhibit the intestinal absorption of zinc and iron (34,35). Our findings are in parallel with the results of the study conducted by Park et al. Zinc deficiency in children leads to morbidity from many diseases such as diarrhea, pneumonia. Diarrhea and pneumonia are still important causes of mortality among children under 5 years of age in developing countries. In this present study, the patients with the co-existence of anemia and zinc deficiency were observed to have recurrent lower respiratory tract infection and diarrhea history. Iron and zinc are the key elements for both physical and mental development of children in the period of rapid growth. Zinc plays a very important role in normal growth and development in human and animal metabolisms through a variety of metalloenzymes and zinc-dependent enzymes. The patients diagnosed with zinc deficiency were observed to have a slowdown in height and weight development. The infants brought to the hospital with the slowdown in growth, loss of appetite and malnutrition complaints are often found to have complementary feeding with low zinc level (such as fruits, vegetables, dairy products and water) in addition to breast milk. These infants also have iron deficiency anemia. Plasma zinc concentration is generally normal in mild zinc deficiency, therefore, normally, it is not recommended to be determinated. In such cases, in addition to the iron deficiency treatment, the implementation of empirical zinc supplementation (1 mg/kg/day) for 1-2 months is recommended. It is difficult to measure the effectiveness of this approach, but the most common clinical result is the improvement in the growth and food intake (36).

However, it was observed in a study conducted that zinc administration in IDA treatment had no positive or negative effect. Therefore, zinc administration was recommended in iron deficiency anemia at different times in addition to iron administration if there was zinc deficiency as well (37). Unfortunately, zinc level is not checked routinely in many centers.

Conclusion

Iron and zinc are the 2 micronutrients that are deficient in the diet of the people of Third World countries. It was found out in this study that 10% of children with iron deficiency anemia had zinc deficiency as well. It is thought that iron zinc combination can be more effective in iron deficiency treatment compared to iron alone treatment, and early period supplementary programs can be useful for high-risk groups such as infant period and early childhood period until zinc deficiency tests give routine values, or to utilize more widely the routine control of serum zinc level is considered to be helpful.

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