

Study of Serum Iron, Copper and Zinc Deficiencies as Etiologic Factors for Nutritional Anemia among School Children

Thesis

Submitted for Partial Fulfillment of Master Degree in Pediatrics

BY

Yasser Mahmoud Awad El Arand

M.B.B.CH 2002

AL-Azhar University

Under supervision of

Prof. Dr. Mohamed Abd El Mohsen El Laboudy

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Prof. Dr. Ahmad Al Saeed Hamed

Assistant Prof. Pediatrics

Faculty of Medicine, Ain Shams University

Dr. Lamis Mohamed Tawfik

Lecturer of Clinical and Chemical Pathology

Faculty of Medicine, Ain Shams University

Ain Shams University

2010

ACKNOWLEDGEMENT

First, I have to thank a mightily ALLAH for giving me help and support to finish this work.

My deepest gratitude to **Prof. Dr. Mohamed Abd El Mohsen El Laboudy**, Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for supervising this work, for his valuable advices and his meticulous guidance.

I am greatly indebted to **Dr. Ahmad Al Saeed Hamed**, Assistant Prof. Pediatrics, Faculty of Medicine, Ain Shams University, for his generous efforts, continuous scientific support and valuable remarks during the preparation of this work.

I would like to express my deep appreciation to **Dr. Lamis Mohamed Tawfik**, Lecturer of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University, for her generous efforts, encouragement and continuous support.

I am also indebted to **Dr. Sayed El-Okda**, Lecturer of Community Medicine, Faculty of Medicine, Ain Shams University, who carried out the statistical analysis through this work.

Deep thankfulness for all children involved in this study, their fathers and mothers.

Finally sincere thanks to my Father, Mother, Wife and all my family, who always support and encourage me.

List of Contents

Objective	Page
INTRODUCTION.....	1
Aim of the work	4
REVIEW OF LITERATURE	5
Anemia: General considerations	5
Definition of anemia	7
Physiologic compensation for decreased RBC mass ...	9
Decreased hemoglobin oxygen affinity.....	9
Redistribution of blood flow	10
Increased cardiac output	10
Clinical signs and symptoms of anemia	11
Classification of anemias	13
Iron deficiency anemia.....	23
Background.....	23
Pathophysiology.....	25
Epidemiology.....	29
Clinical picture.....	34
Medical care.....	50
Complications.....	60
Special concerns.....	64
The role of zinc in child health.....	64
The role of copper in child health.....	75
SUBJECTS AND METHODS.....	92
RESULTS.....	100
DISCUSSION.....	126
SUMMARY AND CONCLUSION.....	152
RECOMMENDATIONS.....	156
REFERENCES.....	157
ARABIC SUMMARY	

LIST OF TABLES

Table No	Table Title	Page
(1)	Normal hematological values during infancy and childhood.	22
(2)	Mineral supplementation of iron	52
(3)	Dietary: Reference intake: Recommended intakes	69
(4)	Copper containing enzymes	76
(5)	Dietary references intakes of copper	78
(6)	Normal plasma concentration of copper and ceruloplasmin	79
(7)	Factor affecting copper absorption	82
(8)	Comparison between anemic and non anemic groups regarding patients' demographic and anthropometric measurements	100
(9)	Comparison between the two studied groups regarding social characterization	102
(10)	Comparison between both studied groups as regard laboratory finding	103
(11)	Comparison between anemic and non anemic as regard Fe, TIBC, Cu and Zinc	104
(12)	Comparison between both studied groups as regard nutritional history data	105
(13)	Correlation between Fe and frequency of consumption different food stuffs among anemic cases	107
(14)	Correlation between Cu and frequency of consumption different food stuffs among anemic cases	108
(15)	Correlation between zinc versus frequency of different food stuffs among anemic cases	109
(16)	Correlation between Fe, Cu and Zinc versus general data among anemic cases	110
(17)	Correlation between Fe, Cu and Zinc versus	112

	CBC parameters among anemic cases	
(18)	Correlation between Fe, Cu and Zinc versus each others among anemic cases	114
(19)	Comparison between both studied groups as regard clinical symptoms and signs suggestive of anemia whatever the type	116
(20)	Correlation between Fe, TIBC, Cu and Zinc and clinical data among anemic cases	118
(21)	Comparison between males and females as regard Fe, Cu and Zinc among anemic cases	119
(22)	Relation between Cu and different clinical findings among anemic cases	120
(23)	Relation between Fe, and different clinical findings among anemic cases	122
(24)	Relation between zinc and different clinical findings among anemic cases	124

LIST OF FIGURES

Figure No	Figure Title	Page
(1)	Illustration of anemia definition	8
(2)	Problems resulting from oxygen extraction in anemic blood	9
(3)	Elimination of red blood cells form the body	17
(4)	Biochemical phenomena which take place during hemolysis	19
(5)	The total body iron in a 70-kg man	24
(6)	Mucosal cells in the proximal small intestine mediate iron absorption	24
(7)	Three pathways exist in enterocytes for uptake of food iron	26
(8)	Both nonheme iron and heme iron have 6 coordinating bonds	40
(9)	Sequential changes in laboratory values following blood loss	41
(10)	The sequence of events (left to right) that occur with gradual depletion of body stores of iron	46
(11)	Ultrastructural studies of the rat duodenum from iron-deficient, healthy, and iron-loaded animals	57
(12)	Comparison between anemic and non-anemic groups regarding nutritional history data	106
(13)	Correlation between Cu versus BMI among anemic cases	111
(14)	Correlation between Fe, Cu and Zinc versus each others among anemic cases	115

LIST OF ABBREVIATION

Abbrev.	Meaning
BMI	Body mass index.
Cog.	Cognitive function.
Cog.Ass.	Cognitive function assessment.
2,3-DPG	2,3-Diphosphoglycerate.
Fe ⁺²	Ferrous form of iron.
Fe ⁺³	Ferric form of iron.
FEP	Free erythrocyte protoporphyrin.
Ferrop	Ferroportin.
Ft	Serum Ferritin.
GV	Growth Velocity.
Hb	Hemoglobin.
Hct	Hematocrit.
IDA	Iron deficiency anemia.
IQ	Intelligence quotient.
IQR	Inter quartile range.
Maxi.	Maximum.
MCH	Mean corpuscular hemoglobin.
MCHC	Mean corpuscular hemoglobin concentration.
MCV	Mean corpuscular volume.
MIDA	Moderate iron deficiency anemia.
Mini.	Minimum.
N	Number.
NID	Non-iron deficient.
P	Predictive.
RB	Reagent Blank.
RBCs	Red blood cells.
RDW	Red blood cell distribution.
S	Standard.
SD	Standard deviation.
Ser-Cu	Serum-copper.
Ser-Zn	Serum zinc.
Ser-Fe	Serum iron.

SIDA	Severe iron deficiency anemia.
Sig.	Significance.
Sys. BP.	Systolic blood pressure.
Tf	Serum Transferrin.
Tf rec.	Transferrin receptors.
TIBC	Total iron binding capacity.
TLC	Total leukocytic count.
U	Unknown.
UIBC	Unsaturated Iron-binding Capacity.
WHO	World Health Organisation.

ABSTRACT

Deficiency anemia is the most prevalent nutritional deficiency in the world. The prevalence of anemia is particularly high in developing countries, where 39% of children under five years old are anemic. The prevalence of IDA in school age children in the Eastern Mediterranean region ranged from 20% in Jordan to 60% in parts of Egypt and Oman. Anemia can cause a variety of complications, including fatigue and stress on body organs. It is often associated with some trace elements deficiencies (iron, zinc, copper). Existing data suggest that iron deficiency anemia (IDA) is a risk factor for poor educational performance in schoolchildren.

Therefore, our study focused on the nutritional anemia and its relationship with iron, zinc and copper. The correlation between anemia and anthropometric measurements, nutritional history and clinical manifestation of anemia was determined. This study was carried out using 200 primary school children (6-12 years old) at Abou-Elada village, Abou-Elmatameer city, El-Behera governorate. Children were chosen by systemic random sample. All children were subjected to: 1. Complete history taking including dietary intake. 2. Physical examination including signs of anemia, growth profile, anthropometric

measurement other vitamin and mineral deficiencies manifestations. 3. Some investigations such as: Complete Blood Count (CBC), serum iron and total iron binding capacity (TIBC) assay, serum copper assay and serum zinc assay.

Results revealed that, 25.5% of the studied children were anemic ($\text{Hb\%} < 11.0 \text{ gm/dl}$) and 74.5% were non-anemic ($\text{Hb\%} \geq 11.0 \text{ gm/dl}$). There is no statistically significant correlation between the anemic and non-anemic group regarding age, sex, weight, height and BMI. In addition, there is no significant difference between anemic and non-anemic regarding the social characteristics (birth order, crowding, family history of anemic and consanguinity).

In respect with the laboratory findings, the MCH, MCHC, MCV, RBCs and TLC were significantly higher in non-anemic group than in anemic group. On the other hand, there is no difference between non-anemic group and anemic group in the platelets count. Iron, Cu and Zn are higher in non-anemic group than in anemic group. On the other hand, the TIBC is higher in anemic group than in non-anemic group.

Regarding nutritional history, while, there were statistically significant differences between the anemic and

non-anemic groups regarding consumed meat, fish, milk, milk products, bread, rice, vegetables and fruits, there was no statistically significant difference between the two groups regarding the consumed eggs. There was a statistically significant positive correlation between Fe versus frequency of meat intake/week, fish intake/week, vegetables intake/day and fruits intake/day. On the other hand, there were no statistically significant correlations between Fe versus egg, milk, milk products, bread and rice intake. There were statistically significant correlations between serum Cu concentrations versus frequency of fish/week, vegetables/day and fruits/day intake. There were statistically significant correlations between Zinc versus frequency of rice/day, vegetable/day and fruits/day intake among anemic cases.

There were statistical significant positive correlation between Cu versus age, BMI and weight among anemic cases. There was a statistical significant inverse correlation between TIBC versus Hb, RBCs, MCH & MCHC, Fe versus TLC, On the other hand, there were statistical significant positive correlation between Fe versus Hb & RBCs, Fe versus MCV and Fe versus MCHC, Cu versus Hb and Cu versus platelets. There were statistical significant inverse correlation between Fe versus TIBC and

a highly significant inverse correlation between Cu versus Zn.

In respect with the studied clinical signs, there were highly significant differences between the anemic and non-anemic groups regarding all studied clinical signs and symptoms. On the other hand, there were significant negative correlations between TIBC versus attention and TIBC versus HR, iron versus attention. There was a statistical significant negative correlation between Cu versus anorexia. There were statistical significant correlations between serum Zn concentrations versus anorexia and diarrhea.

Finally, from these results we can conclude that, the early detection and monitoring of anemia in infants, pre-school and school children is so important. Primary prevention of iron deficiency must be achieved through proper dietary iron intake. Also, oral iron supplementation should be started and continued until the hemoglobin concentration normalizes in anemic children. Copper and zinc supplementation should be administrated in combination with iron in therapeutic doses for anemic children. At a minimum, the hemoglobin concentration should be checked 3 to 4 weeks after beginning oral iron supplementation therapy.

INTRODUCTION

On the basis of information from published and unpublished sources, and the hemoglobin cut-off points recommended by World Health Organization (WHO) scientific group, it is estimated that about 30% of the world's population are anemic. Young children and pregnant women are the most affected, with an estimated global prevalence of 43% and 51 %, respectively. Anemia prevalence among school age children is estimated to be 37% (*DeMayer et al., 1989*).

Most young children living in developing countries consume unbalanced diet that contains low or even negligible haem iron. However, the second type of dietary iron, non-haem iron, is a more important source of iron. It is found to varying degrees in all foods of plant origin. It was found that daily iron requirements are seldom met in the developing countries, and infants and school aged children are therefore at risk for iron deficiency and iron deficiency anemia (*Giovannini et al., 2006*). In fact, iron deficiency anemia is the most common nutritional deficiency of childhood and the most common anemia throughout the world. It presents as microcytic anemia, and is the most common cause of this type of anemia. Serum iron and total iron binding capacity can help differentiate

this type of microcytic anemia from thalassaemia in patients with normal or elevated level of serum ferritin (*Shine, 1997*).

The essentiality of copper for humans was first shown during the 1960s in malnourished children from Peru. These children had an anemia refractory to iron therapy, and bone abnormalities that were responsive to copper supplementation (*Olivares and Uawy, 1996*). Further studies confirmed these findings and established that copper was required for infant growth, host defense mechanisms, bone strength, red and white cell maturation, iron transport, cholesterol metabolism, myocardial contractility, glucose metabolism, and brain development. Major alterations in mental development are also observed in Mink's syndrome, which is a genetic syndrome in which alterations in copper absorption and transport lead to early death. Concentrations of copper in food are highly variable. Organ meats, oysters and chocolate are the richest sources of copper in diet. Human and cow milk are poor sources of copper. The copper content of drinking water is highly variable and is influenced by the natural mineral content and pH of the water and by the plumbing system. Soft acidic water especially if it is conducted through a copper

pip line has a higher copper concentration (***Olivares and Uawy, 1996***).

The most constant clinical manifestation of acquired copper deficiency are anemia, neutropenia, and bone abnormalities. Hematologic changes are characterized by the existence of hypochromic normocytic or macrocytic anemia, which is also accompanied by a reduced reticulocyte count, hypoferrinemia, neutropenia and thrombocytopenia. In a few cases, microcytic anemia is present. In bone marrow, megaloblastic changes, vacuolization of the erythroid, and myeloid progenitors may be found. All of these alterations are reversed through copper supplementation and are unresponsive to iron therapy (***Olivares and Uauy, 1996***).

Zinc is a ubiquitous element that is essential for normal enzymatic function in multiple metabolic pathways. Chronic excessive zinc ingestion causes severe reversible anemia in humans (***Hein, 2003***). Dietary zinc in large doses leads to copper deficiency by antagonizing copper absorption. With discontinuance of zinc, the anemia and hypocupremia are promptly corrected (***Gyorffy and Chan, 1992***). It was found that the combination of iron and zinc improved not only serum ferritin but also hemoglobin. It is generally accepted that both minerals compete for the same