Research Article

Association of Serum Zinc and Copper with Clinical Parameters in Preterm Infants

Sameh S. Fahmey*, Amna G. Mabrouk *, Shimaa A. Abd El-kareem **
and Ahmed A. El-lateef Mahmoud*
* Department of Pediatrics, Faculty of Medicine, Beni-Suef University, Egypt
** Department Clinical Pathology, Faculty of Medicine, Beni-Suef University, Egypt

Abstract
Preterm is defined as babies born alive before 37 weeks of pregnancy are completed. Copper and zinc are essential for the normal growth and development of human fetuses. This study aimed to assess serum zinc and copper levels in 50 single-born preterm infants and their relations with anthropometric parameters at birth in neonatal Intensive Care Unit of Pediatric Department in Beni-Suef University Hospital. All infants were suspected to maternal history taking, full clinical examination with measuring anthropometric parameters including body weight, body length and head circumference, serum Zinc and Copper were measured using spectrophotometer and Complete blood count was done. There was no association between serum zinc levels, serum copper levels and Zinc/Copper ratio with body weight, body length and head circumference. There was no significant correlation between gestational age and serum zinc levels, serum copper levels or zinc/ copper ratio. No significant differences were found between SGA and AGA infants as regarding serum zinc levels, serum copper levels and Zinc/Copper ratio.
Key Words: Preterm– Zinc – Copper.

Introduction

Preterm is defined as babies born alive before 37 weeks of pregnancy are completed. There are sub-categories of preterm birth, based on gestational age: extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), Moderate to late preterm (32 to 37 weeks)[1]. Every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation) and this number is rising. Across 184 countries, the rate of preterm birth range from 5% to 18% of babies born[1]. Preterm birth complications are the leading cause of death among children under 5 years of age responsible for approximately 1 million deaths in 2015[2]. Preterm infants are born at a time of rapid fetal growth when many essential nutrients and minerals are incorporated into the developing fetus. Therefore, premature infants are at a higher risk of nutritional deficiency than full-term infants. The brain is the most highly metabolic organ in preterm infants and consumes the greatest amount of nutrient resources for its function and growth[3]. Preterm birth is often associated with neonatal morbidity. The most frequent diagnoses in preterm infants born with GA less than 27 weeks are perinatal asphyxia and respiratory disturbances resulting in chronic lung disease such as bronchopulmonary dysplasia (BPD), growth failure, patent ductus arteriosis, septicaemia, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH), and/or periventricular leukomalacia (PVL) resulting in neurological sequels and severe brain injury. The morbidity is more severe with a lower GA and BW[4]. **Zinc** is an essential cofactor for more than 300 enzymes, including phosphatases, metalloproteinases, oxidoreductases and transferases. Therefore, Zn plays a key role in protein synthesis, nucleic acid metabolism and immune function[5]. Zinc is needed by every cell in the body as it is responsible for the protein strands in DNA and RNA. As such is crucial for growth and development. A lack of zinc in the diet of a child can be represented as poor growth and development as well as a lack of appetite[6]. Zinc is an essential nutrient for the development of the brain in children. It enhances the cognitive effect by enhancing attention, memory, problem-saving and hand eye coordination. However, the recommended daily amount (10mg) may not be enough to promote the development of most children as it is a recommended amount to prevent deficiencies not improve development[7]. Zinc is also responsible for the enhancement of pituitary hormone function, which is responsible for the release of growth hormone. Growth hormone is responsible for the growth and development of a child, too little can stunt the child's growth, muscular, skeletal, and organs[6]. Zinc is required for laying down tissues during the growth and development of children. Zinc declines in breast milk over time, making it important for breastfeeding mothers to keep replenishing their zinc stores, especially for infants that are preterm or suffering from growth retardation[8]. **Copper** is an essential trace element in both humans and animals. Needed only in trace amounts, the human body contains approximately 100 mg Cu. As a transition metal, it is a cofactor of many redox enzymes. Ceruloplasmin being the most abundant Cu-dependent ferroxidase enzyme has Cu-dependent oxidation activity. Cu plays an important role in iron metabolism and several biological processes including antioxidant defense, neuropeptide synthesis, and immune function [9]. Copper is essential for the normal growth and development of human fetuses, infants, and children[10]. The human fetus accumulates copper rapidly in its liver during the third trimester of pregnancy. At birth, a healthy infant has four times the concentration of copper than a full-grown adult. Human milk is relatively low in copper and the neonate's liver stores fall rapidly after birth due to supplying copper to the fast-growing body during the breastfeeding period[10]. Severe deficiency of copper in pregnant mothers increases the risk of health problems in their fetuses and infants. Health effects noted include low birth weight, muscle weakness, and neurologic problems. However, copper deficiencies in pregnant women can be avoided with a balanced diet [11].

Patients and Methods

This study was performed at the Neonatal Intensive Care Unit of the Pediatric Department in Beni-Suef University Hospital between March 2019 and September 2019. It was a cross-section observational study that included 50 single born preterm infants at birth.

Inclusion criteria:

- Single born preterm infants.
- Sex: both genders will be included.
- Preterm infants born by both Caesarean section and normal vaginal delivery
- Preterm infants with any bodyweight.
- Preterm infants with gestational age (GA) between 23 and 36 weeks. GA was estimated using new Ballard score [12].

Exclusion criteria:

- Infants have major congenital abnormalities.
- Infants have metabolic disorders.
- Infants have ambiguous genitalia.
- Infants born to women with diabetes mellitus, gestational diabetes, chronic hypertension, fever (> 37.8°C), or elevated C-reactive protein (≥ 2.0 mg/dl) before delivery.

Tools:

All infants were suspected to:

- Maternal history including Age, gravidity, parity, delivery history, their last menstrual period, medical disorders as diabetes mellitus, gestational diabetes, chronic hypertension, fever.
- Full clinical examination for all infant including General appearance, Head, including Neck, Skin, Upper limbs, Chest, Abdomen, Genitourinary, Hips, Legs, Feet, Back, Anus, and Neurological examination for detection of dysmorphic features, congenital abnormalities, and metabolic disorders.
- Anthropometric parameters include body weight (BW), body length (BL), and head circumference (HC).
- All parameters were expressed on both the preterm growth chart[13] and the International Postnatal Growth Standards for Preterm Infants [14].
- The following laboratory investigations were done:
    1. Complete blood count
    2. Serum Zn
    3. Serum Cu

Statistical methodology

Data will be statistically described in terms of mean and standard deviation, median, frequencies and relative frequencies (%). Also, the study will be statistically analysis by using tests as t-test for comparison between each group and parametric data, chi-square test will be used. A correlation is a single number that describes the degree of relationship between two variables. The most common type is called the Pearson correlation. A probability (p-value 0 .05>) will be considered statistically significant, statistical package for social science software (SPSS) will be used [15].

Results

The current study was conducted at the Neonatal Intensive Care Unit of the Pediatric Department in Beni-Suef University Hospital between March 2019 and September 2019. It was a cross-section observational study that included 50 preterm infants with a gestational age range from 33-36 weeks (mean 34.8±1.12), maternal age range from 17- 43 years (mean 24.48±6.37), bodyweight range from 1.1-2.5Kg (mean 1.89±0.42), body length range from 38 – 44 centimeters (mean 41.34±1.42) and head circumference range from 27-33centimeters (mean 29.9±1.41).

Table (1): Descriptive laboratory data of the study group

	N	Minimum	Maximum	Mean	Std. Deviation
HGB (g/dL)	50	13.4	19.2	16.54	1.73
RBC ($\times 10^6/uL$)	50	4.08	5.61	4.72	0.37
HCT %	50	42.4	49.1	51.8	5.4
MCV (fL)	50	103.2	117.8	109.87	4.28
WBC ($\times 10^3/ul$)	50	6.2	14.2	10.51	1.48
PLT ($\times 10^3/ul$)	50	143.0	421.0	277.36	48.8
Serum Zn (μg/dL)	50	55.9	179.6	120.5	29.64
Serum Cu (μg/dL)	50	13.7	109.9	79.84	20.44

Table (1) shows serum zinc level range from 55.9-179.6μg/dL (mean120.5±29.64), serum copper level ranges from 13.7-109.9μg/dL (mean79.84±20.44),

Table (2): Correlations between zinc, copper, and copper/zinc ratio and clinical parameters of the studied population.

		Serum Zn	Serum Cu	Zn/Cu
BW	**Pearson Correlation (r)**	-0.02	0.066	-0.006
	Sig. (2-tailed)	0.888	0.647	0.966
BL	**Pearson Correlation (r)**	-0.012	0.19	0.071
	Sig. (2-tailed)	0.934	0.185	0.624
HC	**Pearson Correlation (r)**	-0.129	0.202	0.151
	Sig. (2-tailed)	0.373	0.16	0.295
Gestational age	**Pearson Correlation (r)**	0.042	0.232	0.064
	Sig. (2-tailed)	0.774	0.105	0.656

Table (2) shows there is no significant correlation between serum zinc and copper levels with body weight, body length, head circumference, and gestational age.

Table (3): comparison between SGA and AGA groups as regard zinc and copper levels

	SGA	AGA	p	sig
Serum Zn (μg/dL)	123.3 ± 33.6	118.64± 27.14	0.591	NS
Serum Cu (μg/dL)	82.29± 14.25	78.2± 23.79	0.494	NS
Cu/ Zn	0.73± 0.28	0.69± 0.28	0.427	NS

Table (3) shows no significant differences were found between SGA and AGA groups as regarding serum zinc levels, serum copper levels and Cu\Zn ratio.

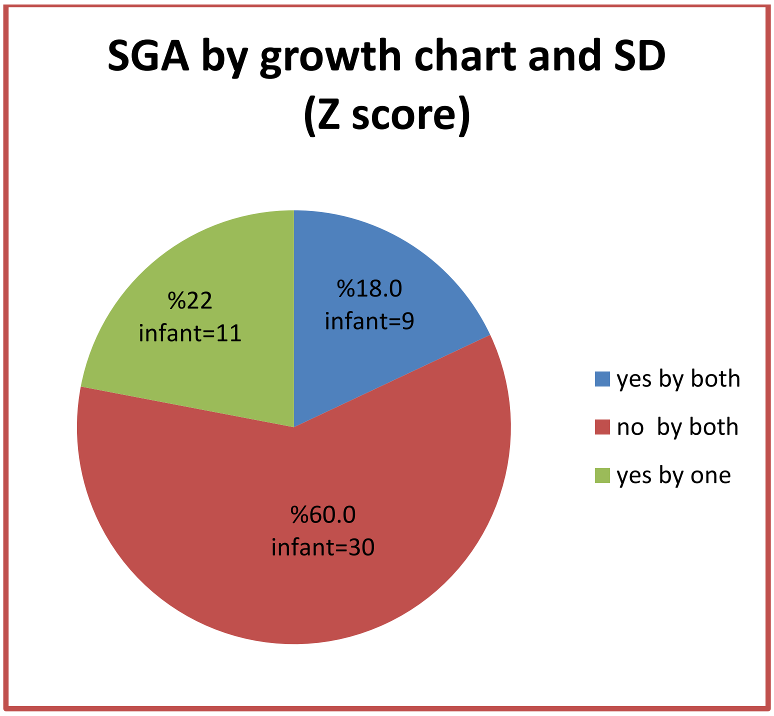

Figure (1): Frequency of SGA in the study population according to preterm growth chart and the International Postnatal Growth Standards for Preterm Infants

Discussion

Preterm infants are born at a time of rapid fetal growth when many essential nutrients and minerals are incorporated into the developing fetus[3]. Zinc is needed by every cell in the body, as it is responsible for the protein strands in DNA and RNA. As such is crucial for growth and development[6]. Zinc is an essential nutrient for the development of the brain in children[7]. Copper is essential for the normal growth and development of human fetuses, infants, and children. The human fetus accumulates copper rapidly in its liver during the third trimester of pregnancy[10]. This study aimed to evaluate the serum levels of zinc and copper in 50 single-born preterm infants and their relations and anthropometric parameters at birth.

In our study there is no significant correlation between serum zinc levels and body weight, body length, head circumference. This agree with Maamouri et al., 2011 who found no significant correlation between serum zinc levels and body weight, body length, head circumference[16]. In contrast with our finding another study was done by Zekavat et al., 2019, which found a significant positive correlation between serum zinc levels and birth weight (r=0.758, P=0.001). Their study was across-sectional study included 107 premature infants[17]. Another study was done by Bayomy et al., 2017 disagree with our study, their study included 80 neonates divided into Preterm neonates (44 neonates) and Full term neonates (36 neonates), they found a highly statistical significant positive relation-ship between serum zinc levels and birth weight (p <0.0001), serum zinc levels and birth length (p <0.0001) and serum zinc levels and H.C (p <0.0001)[18]. Gómez et al., 2015 disagree with our study, they found significant low positive correlation between serum zinc levels and birth weight (p=0.005) was found[19]. Also, Kojima et al., 2017 disagree with our study but their study showed that serum zinc was negatively significantly correlated with body weight, body length, head circumference [20].

In our study, there is no significant correlation between serum copper levels and body weight, body length, head circumference. This agrees with Kojima et al., 2017 who found no significant correlation between serum copper levels and body weight, body length, head circumference[20]. In contrast with our finding another study was done by Zekavat et al., 2019, which found a significant negative correlation between serum copper levels and body weight (r=-0.525, p-value <0.001)[17]. Another study was done by Ozdemir et al., 2007 disagree with our study, their study included 88 infants were categorized as small for gestational age (SGA) (n = 16), the average for gestational age (AGA) (n = 59), and large for gestational age (LGA) (n = 13). They found body weight was negatively correlated with serum copper levels of all groups[21]. Also, Maamouri et al., 2011 disagree with our study but their study showed that serum copper level was significant positively correlated with body weight, body length, and head circumference[16].

In our study there is no significant correlation between zinc/copper ratio and body weight, body length, head circumference. This agree with Kojima et al., 2017 who found no significant correlation between zinc/copper ratio and body weight, body length, head circumference[20]. .Another study done by Maamouri et al., 2011 disagree with our study, they found a significant positive correlation between zinc/copper ratio and body weight, body length, head circumference[16]. The reason for the differences in the outcome of the above studies may be due to the influence of other determinants of clinical parameters apart from serum zinc and copper. Clinical parameters (Birth weight, length head circumference) are determined by both genetic and environmental factors. Therefore variation in these factors among the different studies could explain the differences found[9].

Conclusion

There were no relations between serum zinc levels and serum copper levels in single-born preterm infants with gestational age and anthropometric parameters at birth. No significant differences were found between SGA and AGA infants as regarding serum zinc levels, serum copper levels and Zinc/Copper ratio.

References

1. WHO (World Health Organization). WHO fact sheet on preterm birth. 2018. Available from: http://www.who.int/newsroom/fact-sheets/detail/preterm-birth.
2. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet. 2016; 388(10063):3027-35.
3. Ramel SE, Georgieff MK. Preterm nutrition and the brain. World Rev Nutr Diet. 2014; 110: 190–200.
4. Austeng D, Blennow M, Ewald U, Fellman V, Fritz T, Hellstrom-Westas L , Hellstrom A, Holmgren PA, Hellstrom A; EXPRESS Group. Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in Sweden. Acta Paediatr. 2010; 99(7):978-92.
5. Prasad AS. Zinc in human health: Effect of zinc on immune cells. Mol Med. 2008; 14(5-6): 353–7.
6. MacDonald, R.S. The role of zinc in growth and cell proliferation. J Nutr. 2000; 130(5S Suppl):1500S-8S.
7. Holford P, Colson D. (2010). Food and your child In: Optimum Nutrition for your Child. Piatkus: London.pp.2-55.
8. Bhutta ZA, Hurrell MR., Rosenberg IH (eds). (2012). Meeting Micronutrient Requirements for Health and Development. Kroger Medical and Scientific Publishers: Switzerland. pp.11–26.
9. Bonham M, O'Connor JM, Hannigan BM, Strain JJ. The immune system as a physiological indicator of marginal copper status. Br J Nutr. 2002; 87(5):393–403.
10. Ralph A, McArdle HJ. Copper metabolism and requirements in the pregnant mother, her fetus, and children: a critical review. New York: International Copper Association; 2001.
11. Scheiber I, Dringen R, Julian FB. (2013). Copper: Effects of Deficiency and Overload. In: Astrid Sigel, Helmut Sigel, Roland KO Sigel, editors. Interrelations between Essential Metal Ions and Human Diseases. Metal Ions in Life Sciences 13. Springer. pp. 359–387.
12. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatrics. 1991; 119(3):417-423.
13. Fenton TR & Kim JH. A systematic review and meta-analysis to revise the

Fenton growth chart for preterm infants. BMC Pediatr. 2013; 13:59.
14. Villar J , Giuliani F, Bhutta ZA, Bertino E, Ohuma EO, Ismail LC, Barros FC, Altman DG , Victora C, Noble JA, Gravett MG, Purwar M, Pang R, Lambert A, Papageorghiou AT, Ochieng R, Jaffer YA, Kenndey SH: Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21(st) Project. Lancet Glob Health. 2015; 3(11):e 681-91.
15. Knapp RG, Miller MC. Clinical epide-miology and biostatistics.1992. Published by Williams &Wilkins; Malvern, Pa.: Harwal Pub. Co., C.
16. Maamouri G, Boskabadi H, Noria M, Ayatollahi H, Ghayour-Mobarhan M, Heshmati A, Samirad Z, Mohsenzadeh H. Maternal and Neonatal Zinc and Copper Levels and Birth Weight. Iranian Journal of Neonatology. 2011; 2(1):26-31.
17. Zekavat O, Sahraian A, Esmaili S, Haghpanah S,Rabie S, Alipour F, Bahrami R, Shakibazad N. The Relationship of Birth Weight, Feeding, and Gestational Age with Serum Copper and Zinc in Premature Neonates. Journal of Clinical and Diagnostic Research. 2019; 13(5): SC01-3.
18. Bayomy A, Kassem Y, Younis M, Solaiman A. Cord Serum Zinc Level and Its Impact on Birth Weight, Length and Growth Velocity in the First Three Months of Life. American Journal of Medicine and Medical Sciences. 2017; 7(2): 47-54.
19. Gómez T, Bequer L, Mollineda A, González O, Diaz M, Fernánez D. Serum Zinc Levels of Cord Blood: Relation to Birth Weight and Gestational Period. J Trace Elem Med Biol.2015; 30:180-3.
20. Kojima C, Shoji H, Ikeda N, Kitamura T, Hisata K, Shimizu T. Association of zinc and copper with clinical parameters in the preterm newborn. Pediatrics International. 2017; 59(11):1165–68.
21. Ozdemir U, Gulturk S, Aker A, Guvenal T, Imir G, Erselcan T. Correlation between birth weight, leptin and copper levels in maternal and cord blood. J Physiol Biochem. 2007; 63(2):121‑8.
22. Johnston LB, Clark AJL, Savage MO. Genetic factors contributing to birth weight. Arch Dis Child Fetal Neonatal Ed. 2002; 86(1): F2–F3.