Biological Role and Significance of Copper in Diarrhea

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ABSTRACT

The study was enrolled on (121) subjects, (71) of them with diarrhea and (50) healthy control at ages ranging from 2 month to 5 years. Venous bloods were collected from all patients for the detection of serum copper concentration by spectrophotometric method. It was found that the frequency of lowest concentration of copper 31 (43.7%) in diarrheal cases while the control groups low concentration was only in one case and the percent (2%),these results highly significant (p <0.05).About 23(1.1%) of the dehydrated cases had low serum copper vs. 8(30.8%) of the non- dehydrated, this relation was statistically not significant but important to measure the presence of signs of dehydration ,lows of weight as early detection of the severity or morbidity of diarrhea in children with signs of copper deficiency. Among our patients the mean of copper concentration was (15.3 ±5.8)in male compared with the control group (17.1±3.98) had no significant differences (p>0.05).While in female (14.3 ±5.4) compared with the control group (20.5 ±3.3) statistically significant (p<0.05).The gender differences are due to gender-specific differences in copper trafficking rather than differences in dietary intake. Human body has an elaborate system for managing and regulating the amount of key trace metals. The Correlation between the copper level and hematological status shows that low copper level with low status, also the electrolyte imbalance in diarrheal children with lower (Na+, K+ ,Cl-) concentrations.

Introduction

The human body is composed of elements which can be roughly divided into abundant elements and trace elements.[(1)] Copper is absorbed, transported, distributed, stored, and excreted in the body according to complex homeostatic processes which ensure a constant and sufficient supply of the micronutrient while simultaneously avoiding excess levels.[(2)] However, due to homeostatic regulation, the human body is capable of balancing a wide range of copper intakes for the needs of healthy individuals.[(3)]Many aspects of copper homeostasis are known at the molecular level.[(4)] Copper's essentiality is due to its ability to act as an electron donor or acceptor as its oxidation state fluxes between Cu^{+1}(cuprous) and Cu^{+2} (cupric). Copper is an integral part of the antioxidant enzyme, copper-zinc superoxide dismutase (Cu, Zn-SOD), and has a role in iron homeostasis as a cofactor in ceruloplasmin.[(5)]Excess copper is eliminated mainly through the liver into the bile and is lost through the intestines. A minimal amount is excreted in the urine.[(6)] A copper deficiencies can occur if anyone do not consume an adequate intake of the mineral. Chronic infantile diarrhea is one cause, as well as deficient in copper can also lead to anemia and osteoporosis.[(7)]. Most diets contain enough copper (2-5mg daily) to prevent a deficiency and not enough to cause toxicity. The World Health organization (WHO) suggests that 10-12mg per day may be the upper safe limit

for consumption, copper toxicity is usually due to: excessive supplementation. The increasingly common problem of low levels of zinc in the diet, contaminated food and drinking water outstanding to connection with metallic copper.[8]The anemia caused by copper deficiency is thought to be caused by impaired iron transport. Hephaestus is a copper containing ferroxidase enzyme located in the duodenal mucosa that oxidizes iron and facilitate its transfer across the baso lateral membrane into circulation.[9]Ceruloplasmin also oxidizes iron from its ferrous state to the ferric form that is required for iron binding.[10]Electrolytes are minerals that affect the amount of water in the body, muscle function, and the acidity of the blood. Its complications remain a major cause of morbidity and mortality in children under five years of age worldwide and is responsible for 2.4 million deaths each year.[11]

Methods

This is a hospital-based, case control study conducted in special pediatric hospital and Azadi hospital in Kirkuk from April, 2015 to end of September, 2015. The study was enrolled on 121 subjects, 71 of them with diarrhea and (50) healthy control at ages ranging from 2 month to 5 years. Fifty normal healthy children 25(50%) female & 25(50%) male assessed by specialist were selected randomly as a control group, with the same exclusion criteria of the patient. They were almost similar to patients in age ranges, sex, occupation and their residence. Venous blood samples 3-5 ml were obtained from patients, and control groups, then is divided into two tubes, one tube with EDTA for doing CBC(complete blood count) investigation, and another tube without EDTA for doing copper and electrolytes investigation.

The principle of copper determination based on, releasing the copper from ceruloplasmin in an acidic medium, reacts with Di-Br-PAESA to form a coloured complex. Intensity of the complex formed is directly proportional to the amount of copper present in the sample.

HumaLyte Plus 5 Bench top ISE Electrolyte Analyzer, brand (monash international), model (EA-5).The potentiometric techniques measure the potential difference between two electrodes. Specific electrodes are used for the determination of sodium, potassium and chlorides. The requirement is for an ion selective membrane to separate the solution of known activity from the detecting system. The membrane consists of special glass, a disk of crystalline material or an organic ion exchanger saturating a water-immiscible solvent held in a gel or plastic. The sodium electrode is sensitive to changes in sodium ion concentration and potassium electrode is sensitive to changes in potassium ion concentration.

TOKYO, JAPAN - Nihon Kohden Corporation introduces Celltac Alpha MEK-6400 series hematology analyzers. These fully automated hematology analyzers have 18 parameters, 3-part WBC differential and panic values.

Results The mean copper level among male cases was (15.3±5.8)µg/dl vs. (17.1±3.98)µg/dl, this relation was statistically not significant, while among females was (14.3 ±5.4)µg/dl, vs.(20.5±3.3)µg/dl among controls this relation was statistically significant , as shown in table (1).

As serum copper normal value differ among male (11-22µg/dl) and female (12.58-24.8µg/dl), the data was named low , high and normal depending on gender value for each subject . The serum copper was found among 31(43.7%) of the cases vs. 1(2%) of the controls, this relation was statistically significant as shown in table (2).

About 23(1.1%) of the dehydrated cases had low serum copper vs. 8(30.8%) of the

non- dehydrated, this relation was statistically not significant as shown in table (3).

About 19(42.2%) of the wasted cases had low serum copper vs. 12 (46.2%) of the non- wasted, this relation was statistically not significant as shown in table (4).

About 23(41.8%) of the normal weighted cases had low serum copper vs. 7 (50%) of the under -weight, this relation was statistically not significant as shown in table (4).

Most of the diarrheal and control cases were male 43(60.6%), 25(50%) respectively, compared with female 28(39.4%), 25(50%) respectively, this relation was statistically not significant, as shown in table (5).

The distribution of serum copper level according to the electrolytes concentration in the study groups were studying**,** those who had low copper level and low K level among cases was 21(67.7%), vs. 9(29%) had normal K level. While those who had low copper level and low Na level among cases was 17(54.8%), vs. 13(41.9%) had normal Na level, Moreover, Those who had low copper level and low Cl- level among cases was 19(61.3%), vs 9(29%) had normal Cl level, and those who had low copper level and low Ca level among cases was 0(0%), vs. 1(100%) had normal Ca level as shown in table (6).

Effects of diarrhea on hematological status in children as the blood picture normal values depend on the age; therefore the age was taken in consideration in dividing the values normal low and high among each age group as shown in table (7).

The hematological status in diarrheal children with low copper level was studying as shown in table (8). Which demonstrated that those who had low copper level and low Hb count level among cases was 26(83.9%), vs. 5(16.1%) had normal Hb level, while those who had low copper level and low PCV level among cases was 18(58.1%), vs. 13(41.9%) had normal PCV level, moreover, those who had low copper level and low WBC level among cases was 4(12.9%) vs. 24(77.4%) had normal WBC level and those who had low copper level and low platelet count among cases was 3(9.7%) vs. 26(83.9%), had normal platelet count this relation was statistically not significant as shown in table (8).

Regarding the correlation between the serum copper level with the different serum electrolyte levels and blood pictures, the results represent that there were significant moderate positive correlation between copper level and WBC count 0.33 (when copper increased the WBC increased) among diarrheal cases. There were no correlation between copper and different variables among controls, while when analysis of total data regardless of having diarrhea or not it represent that there were moderate positive correlation with Hb 0.3 and weak positive relationship with the PCV value, as shown in table (9), figures 1, 2 ,and 3.

correlation was done according to age, and results represents that at age of 2 months there were non- significant strong negative correlation with PCV -0.44, and strong positive correlation with WBC 0.489, among 3-6 months there were non-significant moderately positive correlation with Hb 0.33, and PCV 0.32, while there were negative moderate correlation with platelet count-0.37. among those aged >12, as shown in table (11) .

Discussion

The demographic picture of studied group in table (1) reveals that the majority of the diarrheal and control cases were male 43(60.6%), 25(50%) respectively, compared with female 28(39.4%), 25(50%) respectively as shown in figure (1). This frequency is comparable, to some extent, with that of local previous studies in Iraq (Noaman,. 2013)[12] and, (Shakir and Hussein)[13] and that for Tanzania(Moyo et al., 2011).[14]The results that previously mentioned denoted that-high frequency among males rather than females which may be due to the region that the cultural background of our cases that care for male than female. The boys would be affected more compared to girls deserves further exploration and attention in terms of interventions. Most cases is shown the gender is effected on the level of copper, the male was (15.3±5.8) µg/dl vs. controls (17.1±3.89) µg/dl and female was (14.3± 5.4) µg/dl,vs.(20.5± 3.3) µg/dl as shown in table (2), this result in agreement with(Rosanna Squitti 2011)[15]and(Clark et al.2007)[16] which have found an effect of gender on serum copper, higher copper levels in female than in male.The gender differences are due to gender-specific differences in copper trafficking rather than differences in dietary intake. Human body has an elaborate system for managing and regulating the amount of key trace metals.[17]The percentage of the lower level were (43.7%) when compared with control as display in table (3), this result in agreement with (. Khare, et al., 2012)[18], and (Nurinnisa Öztürk et al. 2015)[19] few cases have a high level of copper this result in agreement with (Geir Bjørklund 2013)[20] and (Hassan et al. 2014)[21].

Copper deficiency may be due to reduction in ceruloplasmin in children, which is attributed to its excessive loss or destruction or inability to synthesis leading to lack of copper transport to the liver, copper deficiency has been attributed to losses, inadequate intake and poor bioavailability. Serum Cu levels increase with age and reach adult levels by 6 months of age, the levels in infants in the 2 month were lower than those at 6 and 12 months.[19]Copper level very important to our immune system, due to the association of copper in many enzymes structures, and also the important role of them in the immune system. Moreover abnormally elevated Cu concentrations can cause oxidative damage to lipids, nucleic acids and proteins.[20]

The distribution of diarrheal cases according to the copper level and weight of child were investigated and shows no effect of copper on the weight of child about 23(41.8%) of normal weighted cases had low serum copper vs.7(50%) of the underweight this shown in table (6)this result in agreement with (Özden, et al., 2015)[22] and disagreement with (Marquardt ,et al 2012)[23]. Infants with low birth weight most common in copper deficient and young children with diarrhea. lacking copper can be effect on growth and development in children. Deficiency in one trace element may impair absorption of another Cu deficiency impairs Fe absorption. There is also a strong interaction between Zn and Cu, and they compete at the level of intestinal absorption high Zn levels in the diet can reduce the absorption of Cu, but high dietary Cu does not decrease absorption of Zn. Infants and babies with low birth weight may therefore be at risk of copper deficiency.[22,24]

Copper levels can be evaluated to help diagnose several disease processes. Most cases indicate a decrease in potassium K level as illustrated in table (7). It is concluded that diarrhea is a well-known cause of hypokalemia; stomach acid has a high concentration of potassium, in the form of potassium chloride. Potassium is

important in the stomach for the production and secretion of acid, which helps in the digestion of the foods we eat. When a child has diarrhea, the stomach contents get flushed out of the gastrointestinal tract into the stool and out of the body, taking with it a large amount of potassium and causing hypokalemia. Calcium, chloride and sodium are all electrolytes, during prolonged fluid loss will decrease(Lindinger & Ecker., 2013).[25]Sodium is found mostly in the body fluids outside the cells, is also necessary for the transmission of electrochemical impulses along nerve and muscle membrane. Low sodium can be caused by diarrhea, kidney diseases, sweating, and vomiting.[26]Most cases shows no influence of lowering copper level on the Cl^- level. This result is in disagreement with (Soetan, et al., 2010)[27]. Too little chloride occurs parallel with other electrolyte disorders, specifically hyponatremia and hypokalemia as shown in table (8).

The hematological status in diarrheal children with low copper level were studying as shown in table (9)reveals that the low blood counts are due to nutritional deficiencies or blood loss to total body blood volume or decrease in production of RBC or Hb. The Hb decreased when compared with that of the controls this result is in agreement with(Mohammad and Omer, 2011)[28]the age from 3-6 month and 6-12 month had low Hb level while this result in disagreement with(Manju and Ismail 2012)[29]anemia prevalence of approximately 80% in children aged between 6 and 36 months.[30] There was a decreasing in the mean of PCV of the cases when compared with control group this result in agreement with (Mallouh , et al. 2015)[31] the age from 3-6 month and 6-12 month had low PCV level, this result in disagreement with(Adaay et al. 2011)[32] there was a decreasing in the mean of WBC of the cases when compared with control group this result in disagreement with (Jong Duck Kim 2013)[33] and (Xu , et al. 2013)[34].
WBC was higher in cases compared to control. The low WBC is due to infections that use active white blood cells faster than they can be produced, also drugs that used destroy white blood cells due to the function of white blood cells, or leukocytes, is to fight infection and help to protect the body by a process called phagocytosis this is when the WBC surrounds and destroys a foreign cell. Most cases shows an intensification of Platelet in the cases when compare with control children this show in table (9) this frequency is comparable, to some extent, with (Shin, et.al 2015)[35]and disagree with (Celik et al.2014)[36] and (Öztürk et al.2013)[37].Increase Platelet due to recovery from serious blood loss, acute infection or inflammation, or response to physical activity. The age not effected on the level of Platelet levels and also no difference between girls and boys. [36]
The correlation between the copper level and different blood count and electrolyte levels among cases and controls were illustrated in table (10) shows a liner correlation as demonstrated in figure (2) between WBC and copper level among diarrheal cases which reveals that when copper increased WBC increased, while the liner correlation in figure (3) between Hb and copper level among total study sample shows there were moderate positive correlation with Hb, and in figure (4) shows a weak positive relationship with the PCV value.

The correlation was done according to age this shown in table (11) and results represents that at age of 2 months there were non- significant strong negative correlation with PCV r-value = -0.44, and strong positive correlation with WBC r= 0.489, among 3-6 months there were non-significant moderately positive

correlation with Hb r-0.33, and PCV r=0.32, while there were negative moderate correlation with platelet count r=-0.37. among those aged >12 months there were significant moderately positive correlation with Hb r= 0.387, and PCV 0.r= 329, which mean that copper had more affected and affect Hb levels this result in agreement with (Guo and Chen, 2011)[38], and PCV levels this result in agreement with (Akanni, et al.,2012)[39] during the age of > 12 months as shown in table (11).

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الخلاصة :تضمنت الدراسة الحالية مئة واحدى وعشرون مريض من الاطفال أعمارهم ما بين شهرين الى خمس سنوات احدى وسبعون طفل يعانون من الإسهال أجريت لهم المقارنة مع مجموعة السيطرة وكان عددهمخمسون من الأطفال الاصحاء، حيث تم جمع نماذج الدم منهم وفصلت المصول لقياس مستوى النحاس باستخدام جهاز المطياف الضوئي. وجد انخفاض مستوى النحاس في الاطفال المصابين بالإسهال وكانت نسبة الانخفاض 31(43.7%) في حين لم يسجل انخفاض في مجموعة السيطرة الا في حالة واحدة وكانت النسبة (2%) مما يدل على وجود فرق معنوي (05≥) ،اعلى نسبة للإصابة بالجفاف نتيجة الاسهال المصحوب بانخفاض مستوى النحاس كانت 23(1.1%) في حين كانت 8(30.8 %) لا يعانون من الجفاف و هذه النتائج لا تحمل مدلول احصائي ولكنها مهمة للتشخيص المبكر ولمعرفة خطورة الحالة المرضية .كما أظهرت النتائج ان معدل النحاس في الذكور كان (15±5.8) بينما في مجموعة السيطرة (17.1±3.98) بينما في الاناث كان (14.3 ±5.4) بينما في مجموعة السيطرة (20.1 ±3.3) مما يؤكد وجود فرق معنوي (05 ≥) . ومن هذه النتائج نستدل ان النحاس ينخفض في الاطفال الذي يعانون من الاسهال ويجب ان يعوض في الغذاء الاعتيادي او التكميلي. أن الفرق بين الاجناس يعزى لوجود فرق بجينات السيطرة الموجودة في داخل الجسم المنظمة لتراكيز العناصر الشحيحة بشكل عام وليس لسبب فروقات التغذية. كما أثبتت الدراسة أن انخفاض مستوى النحاس مصحوب بانخفاض في مستوى الكتروليت الدم وصورة الدم كاملة.

Table (1): The mean copper level according to the gender among cases and controls

Gender	study groups	N	Mean µg / dl	Std. Deviation	t, P value
Male	Case	43	15.3	5.8	
	Control	25	17.1	3.98	1.4, > 0.05
Female	Case	28	14.3	5.4	4.9, < 0.05 S
	Control	25	20.5	3.3	

Table (2): The distribution of study groups according to the copper level

copper level	study groups		Total
	Case	Control	
Low	31	1	32
	43.7%	2.0%	26.4%
High	5	4	9
	7.0%	8.0%	7.4%
Normal	35	45	80
	49.3%	90.0%	66.1%
Total	71	50	121
	100.0%	9100.0%	100.0%

X^2=26.644, df= 2, P value < 0.05significant

Table (3): The distribution of diarrheal cases according to the copper level and dehydration

copper level	Dehydration		Total
	Yes	No	
Low	23	8	31
	51.1%	30.8%	43.7%
High	2	3	5
	4.4%	11.5%	7.0%
Normal	20	15	35
	44.4%	57.7%	49.3%
Total	45	26	71
	100.0%	100.0%	100.0%

X^2=3.326, df= 2, P value > 0.05 not significant

Table (4): The distribution of diarrheal cases according to the copper level and Weight of child

Copper level	Weight of child:			Total
	Normal	Under weight	Obese	
Low	23	7	1	31
	41.8%	50.0%	50.0%	43.7%
Hih	5	0	0	5
	9.1%	.0%	.0%	7.0%
Normal	27	7	1	35
	49.1%	50.0%	50.0%	49.3%
Total	55	14	2	71
	100.0%	100.0%	100.0%	100.0%

X^2=1.647, df= 4, P value > 0.05 not significant

Table (5): The distribution of study groups according to gender

Gender	study groups		Total
	case	control	
Male	43	25	68
	60.6%	50.0%	56.2%
Female	28	25	53
	39.4%	50.0%	43.8%
Total	71	50	121
	100.0%	100.0%	100.0%

X^2=1.33, df= 1, P value > 0.05 not significant

Table(6): The distribution of serum copper level according to the electrolytes concentration in the study groups

study groups		copper code			Total	
		Normal	low	high		
K^+	Low	7 (20.00%)	9(29.00%)	2(40.00%)	18(25.40%)	2.74, >0.05
	Normal	28 (80.00%)	21(67.70%)	3(60.00%)	52(73.2 0%)	
Na^+	Low	12(34.30%)	13(41.9 0%)	3(60.00%)	28(80.00%)	1.62,>0.05
	Normal	21(60.00%)	17(54.80%)	2(40.00%)	40(56.30%)	
Cl^-	Low	8 (22.90%)	9(29.00%)	1(20.00%)	18(25.40%)	1.42,>0.05
	Normal	25 (71.40%)	19 (61.30%)	4 (80.00%)	48 (67.60%)	
Ca^{2+}	Low	5(14.30%)	8 (25.80%)	1 (20.00%)	14(19.70%)	
	Normal	29 (82.90%)	23 (74.20%)	4 (80.00%)	56 (78.90%)	2.29,>0.05

Table (7): The distribution of hematological status in the study groups

Age	Hb	PCV	WBC	Platelet
	Mean±SD	Mean±SD	Mean±SD	Mean± SD
2 months	10.08±1.6	31.20±5.3	10.6±4.3	392.6±196
3-6 months	9.81±0.82	30.09±2.5	11.6±5.3	375.6±139
6-12 months	9.82±1.27	29.7±5.8	10. ±4.0	328.6±106
> 12 months	10.25±1.44	31.5±3.9	10.6±4.1	343±110
t, P value	2.97,<0.055	1.15, > 0.05	0.92, > 0.05	0.026,>0.05

Table (8): The distribution of copper levels and hematological status in the study groups

study groups		copper level			Total	X^2, P value
		Normal	Low	high		
Hb	Normal	4 11.40%	5 16.10%	2 40.00%	11 15.50%	
	Low	30 85.70%	26 83.90%	3 60.00%	59 83.10%	3.7, >0.05
PCV	Normal	15 42.90%	13 41.90%	4 80.00%	32 45.10%	
	Low	20 57.10%	18 58.10%	1 20.00%	39 54.90%	2.65, >0.05
W.B.C	Normal	25 71.40%	24 77.4%	2 40.00%	51 71.80%	
Platelet	Low	4	4	0	8	7.9, >0.05

		11.40%	12.90%	0.00%	11.30%	
	Normal	26 74.3%	26 83.9 0%	5 100.00%	57 80.3 0%	2.76, >0.05
	Low	7 20.00%	3 9.7 0%	0 0.00%	10 14.1 0%	

Table (9): The correlation between the copper level and different blood count and electrolyte levels among cases and controls

Variables	S. Copper (r)		
	Case	control	Total
K^+	0.2	-0.02	0.15
Na^+	0.01	0.02	0.11
Cl^-	-0.07	0.01	0.05
Ca^{2+}	0.17	-0.14	0.08
HB	0.12	0.1	0.3**
PCV	0.16	-0.02	0.2*
WBC	0.330**	-0.003	0.2
Plt	0.07	-0.15	-0.02

*** correlation is significant at 0.05 level, ** correlation is significant at 0.01 level**

Table (10): The correlation of the serum copper level and blood picture according to age

Age	Blood count	S. Copper (r)
2 months	**HB**	**0.051**
	PCV	**-0.441**
	WBC	**0.489**
	Plt	**-0.045-**
3-6 months	**HB**	**0.332**
	PCV	**0.323**
	WBC	**0.196**
	Plt	**-0.371-**
6-12 months	**HB**	**0.24**
	PCV	**0.276**
	WBC	**0.146**
	Plt	**0.188**
> 12 months	**HB**	**0.387***
	PCV	**0.329***
	WBC	**0.132**
	Plt	**-0.149**

***. Correlation is significant at the 0.05 level (2-tailed).**

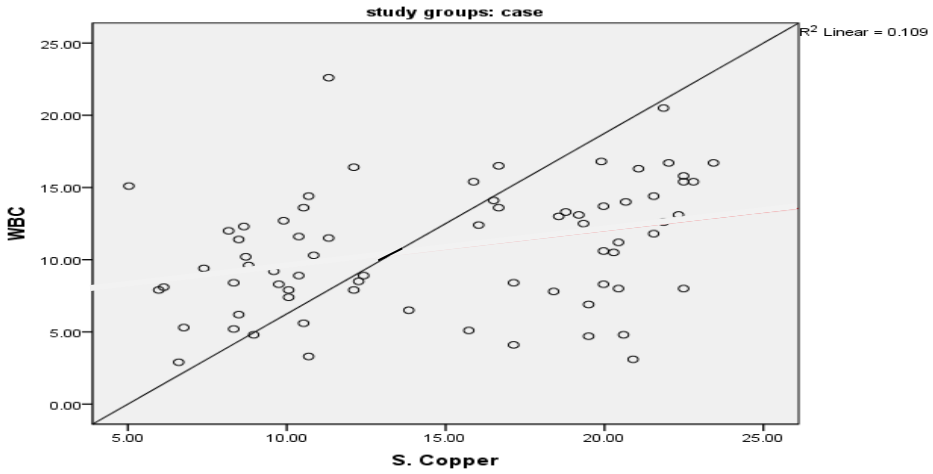

Figure (1) The linear correlation between WBC and copper level in diarrheal cases

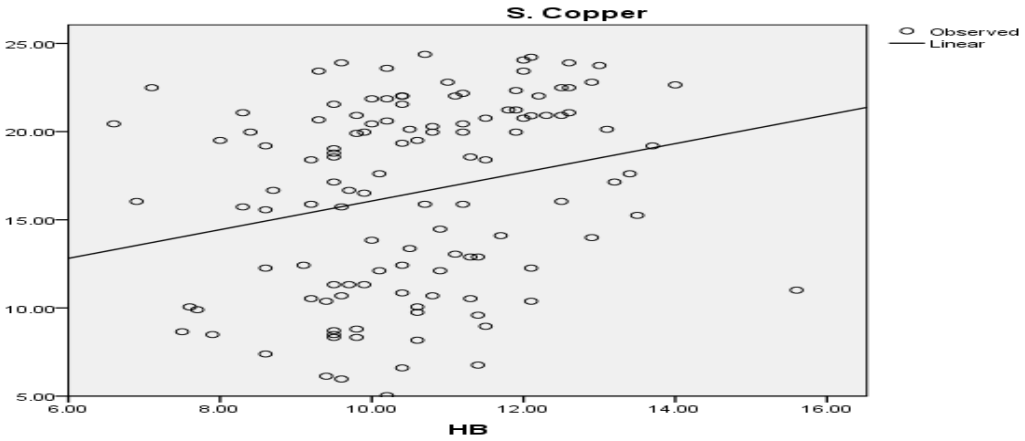

Figure (2): The linear correlation between Hb and copper level among total study sample.

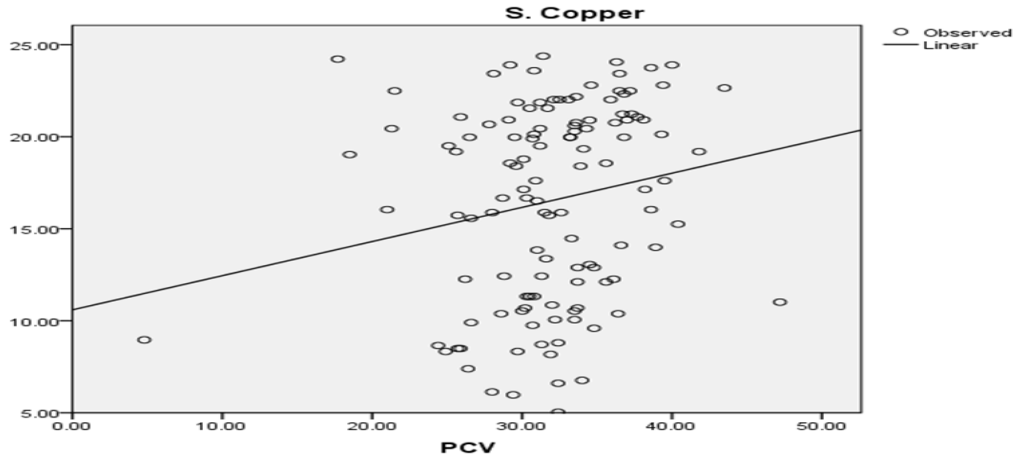

Figure (3): The linear correlation between PCV and copper level among total study sample.