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The Association between Elevated Serum Copper (Cu) Levels and Its Complications in Cu T380a IntrauterineDevice (IUD) Users; a Cross-Sectional Study

Alaa Mohamed Atef*, Maher Omran, Waleed Elbasiony,
Marwa Adham, Noha Nasr, Walaa Elsayed, Mortada Elsayed
Obstetrics and Gynecology Department, Faculty of Medicine, Ain Shams University, Egypt
***Corresponding author:** Alaa Atef, **Mobile:** (+20) 01001886343, **E-mail:** dralaamatef@gmail.com

ABSTRACT

Background: While it is widely recognised that intrauterine devices (IUDs) do not usually cause copper toxicity, there have been documented instances. The likelihood of copper poisoning from an IUD is somewhat increased in women with chronic liver illness because it may impair their body's capacity to metabolise minerals like copper.

Objective: This study aimed to evaluate the correlation between the use of copper T380A IUD and levels of copper in blood in Cu IUD users through measuring their blood copper level and to assess potential Cu toxicity.

Patients and methods: A total of 159 women using copper T380A IUD as a method of contraception were enrolled and subdivided into 3 equal groups: Group A included women using copper T380A IUD ≥ 1 year, group B included women using copper T380A IUD less than 1year and group C "non-users" "control group" included women not using copper T380A IUD as a method of contraception, with the same inclusion and exclusion criteria. All cases were asked about symptoms of Cu toxicity using case report form and questionnaire as gastric upset, nausea, vomiting, diarrhea, change in colour of stool, bloody or black stools, headache, lightheadedness, fatigue, elevated body temperature or chills, myalgia, palpitations, changes in taste up to anorexia, mood swings, symptoms of depression or anxiety, irritability, hardly focusing and body system failure. Incidence and prevalence of Cu toxicity symptoms were evaluated and cutoff point of serum copper level in µg per deciliter and its correlation with Cu toxicity was assessed.

Results: No differences were noted between study groups regarding serum Cu level 108.46 ± 22.93 vs. 104.13 ± 22.44 vs. 109.15 ± 22.66 µg/dl and symptoms of Cu toxicity except fatigue and tachycardia that were more frequent among control group with no significant clinical value. Also, no differences were noted between study groups regarding maternal age and BMI. **Conclusion:** There was no rise in blood copper levels among IUD users, regardless of duration of usage. Copper T380A IUD is recommended to be used safely without danger of Cu toxicity.

Keywords: Serum copper, Cu T380a IUD, Cu toxicity.

INTRODUCTION

One of the most popular methods of birth control is the copper Cu-IUD, which is inexpensive, effective, and has a long-lasting impact [(1)]. To make Cu-IUDs, T- or U-shaped flexible polymer material is usually wrapped around Cu wires or tubes [(2)]. Because they stimulate the endometrium to secrete prostaglandins and leukocytes, which reduce the endometrial's receptivity to embryo implantation, Cu ions from a Cu-IUD are helpful for contraception [(3, 4)]. Because Cu ions emitted from Cu-IUDs are cytotoxic to the cells in the implant site. It has also been linked to cytotoxicity towards distant organs such as the kidney, liver, spleen, and lungs [(5)].

Recently, there has been a lot of focus on the potential toxicity of Cu ions, especially when exposed to the body over a prolonged length of time [(6)]. There is insufficient evidence on the potential systemic toxicity of Cu-IUDs, hence more research is required. It is also expected that Cu-IUDs' safety evaluation will aid in their widespread use. Therefore, our study's objectives were to assess potential Cu toxic effects and the relationship between copper T380A IUD use and blood copper levels in Cu IUD users by measuring their blood copper levels.

SUBJECTS AND METHODS

This cross-sectional study was conducted at Family Planning Outpatient Clinic, Obstetrics and Gynecology Department, Faculty of Medicine, Ain Shams University Maternity Hospitals from December 2022 until May. Our study was conducted on 159 women using Copper T380A IUD as a method of contraception attending Ain Shams University Maternity Hospital. They were subdivided into 3 equal groups: Group A "long standing", women used copper T380A IUD ≥ 1 year. Group B "recent users", women used copper T380A IUD < 1year. Group C "non-users" "control group", Women didn't use Copper T380A IUD as a method of contraception.

Inclusion criteria: Non pregnant women, aged between 18-45 years old with BMI 25-35 kg/m^2 and welling to participate in the study.

Exclusion criteria: Women using copper containing supplements or women with medical conditions that reduce the liver's ability to remove excess copper from the body as genetic diseases affecting Cu homeostasis (e.g. Wilson's disease and Menkes disease), liver disease e.g. hepatitis, diabetes mellitus, Hodgkin lymphoma, leukemia, brain, liver or breast cancer.

Study interventions and procedures: All patients enrolled to our study were subjected to comprehensive history taking including personal, menstrual, obstetric, contraceptive and past history.

All cases were asked about symptoms of Cu toxicity using case report form and questionnaire as gastric pain, nausea, vomiting, diarrhea, blue- or green-colored stool, dark, sticky stool containing blood, headache, dizziness, fatigue, fever or chills and aching muscles. Extreme thirst, tachycardia or abnormally fast heart rate, changes in taste that could

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lead to decreased appetite or anorexia, sudden changes in mood, symptoms of depression or anxiety, feeling irritable or overexcited, difficulty focusing, kidney failure, heart failure, loss of red blood cells and liver failure or brain damage. To ensure confidentiality, only the patient initials were recorded in the case report form, and when the patient's name appeared on any other document, it was kept in a secure place by the investigators (Table 1).

The investigators maintained a personal patient identification list (Patient initials with the corresponding patient names) to enable record to be identified. This was followed by general and local examination. Ultrasound was done to confirm presence and position of Cu T380A IUD in the IUD users. Then serum copper level was measured to all the patients enrolled in the study. 2 ml blood was collected in heparinized sample vials by a nurse and kept in refrigerator until analysis. Briefly, blood was lysed with 1% Triton X-100 solution (Sigma-Aldrich, St. Louis, MO, USA). At pH of 4.7 copper was released from the carrier protein and formed with 4-(3.5-Dibromo-2-pyridylazo)-N-clhyl-N-sulfopropylaniline a chelate complex. The increase of absorbance of this complex was measured and proportional to the concentration of total copper in the sample.

Assay procedure:

- Wavelength: 580 run
- Temperature: 37°C
- **Pipette into cuvette:**

	Standard	Sample
Reagent	1000 µl	1000 µl
Serum or plasma	-	50 µl
Standard	50 µl	-

- Mix and incubate for 5 minutes al 37 °C.
- Measure the absorbance of the sample $A_{(s)}$ and of the standard $A_{(STD)}$ against the reagent blank $A_{(RBL)}$

$$\delta A_{(s)} = A_{(s)} - A_{(RBL)}$$
$$\delta A_{(CAL)} = A_{(CAL)} - A_{(RBL)}$$

Calculation:

$$c = 100 \times \frac{\delta A_{(S)}}{\delta A_{(CAL)}} \quad (\mu g/dl)$$

Table (1): Case record form

Personal History	Date of current marriage:	Address:
	Name:	Occupation:
	Age:	Special habits:
	Pr. Marriage:	Offspring's:
Present History "onset, course and duration of symptoms of Copper toxicity":	Gastric upset, Nausea and vomiting, Diarrhea, Change in colour of stool, Bloody or black coloured stools, Headache, Lightheadness, Fatigue,	
	Elevated body temperature or chills, Myalgia, Palpitations, Changes in taste up to anorexia, Mood swings, Extreme thirst, Symptoms of depression or anxiety, Irritability, Hardly focusing, Organ failure: e.g. Kidney, Heart, Liver or Brain Hemolysis	
Menstrual History	L.M.P: Regularity: Duration: Amount of blood loss: G.A.:	
Past History	History of: Medical disorders Medications or allergy Exposure to radiotherapy for malignancy Pelvic inflammatory disease Peritonitis Any abdominal or pelvic surgery for non-obstetric cause e.g. cancer or endometriosis.	
Contraceptive History	Methods used before and complications reported.	
Obstetric History	Gravidity: Parity: Abortions: Living: Mode of delivery: Date of the last delivery: History of congenital fetal malformation: Contraindications for vaginal delivery: Previous obstetric complications as prolonged labor, sepsis, etc:	
Medical History	About medical conditions that reduce the liver's ability to remove excess copper from the body: History of medications:	
Surgical History	Previous surgeries:	
General Examination	General appearance: BMI Complexion Vital signs	
Abdominal Examination	Presence of mass	
Local Examination	Vulva: Vagina: Cervix: Uterus:	

Study outcomes:

Primary outcome: Incidence and prevalence of Cu toxicity symptoms.

Secondary outcome: Cutoff point of serum copper level in µg per deciliter and its correlation with Cu toxicity.

Ethical approval: The ethics committee of Ain Shams University's Faculty of Medicine approved the study. After completing the eligibility criteria and before being recruited in the study, all patients provided informed written consents as permission to participate after the nature, scope, and potential implications of the study were described to them in a comprehensible manner. The Helsinki Declaration was observed throughout the study's duration.

Statistical analysis:

The recorded data were analysed using SPSS version 23.0. For the numerical data, the ranges and mean ± SD were shown. Numeric values and percentages were also displayed for quantitative variables. Data were checked for normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. ANOVA was utilised when comparing more than two means. Post Hoc-test was used. When comparing several variables at once, Tukey's test was employed. When the predicted count in any cell was less than 5, the X^2-test and Fisher's exact test were used to compare groups with qualitative data rather than the Chi-square test. A margin of error of 5% was acceptable, and a confidence interval of 95% was established. When it is equal to or less than 0.05, a significant p-value is taken into account.

RESULTS

Our study showed no statistically significant difference between groups according to demographic data about age and BMI, with p-value ($p > 0.05$) (Table 2**)**.

Table (2): Comparison between groups according to demographic data

Demographic data	Group A (n=53)	Group B (n=53)	Group C (n=53)	F-test	P-value
Age (years)					
Mean ± SD	31.15 ± 9.04	30.25 ± 7.85	31.40 ± 8.27	0.276	0.759
Range	18-45	18-45	18-45		
BMI [wt/ (ht)^2]					
Mean ± SD	28.44 ± 2.47	29.03 ± 2.72	28.13 ± 2.38	1.730	0.181
Range	25-33.7	25-35	23.4-33		

Data are expressed as Mean ± SD Using: F-One way Analysis of Variance test p-value>0.05 is insignificant.

We also concluded higher frequency of fatigue and tachycardia in group C (non IUD users) than in groups A & B (with $p < 0.05$). While, there was no statistically significant difference between groups according to the rest of general symptoms ($p > 0.05$), this indicates that the no association between CuT380A IUD and general symptoms **(**Table 3**)**.

Table (3): Comparison between groups according to general symptoms

General Symptoms	Group A (n=53)		Group B (n=53)		Group C (n=53)		x^2	p-value(FE)
	No.	%	No.	%	No.	%		
Stomach pain	4	7.5%	2	3.8%	8	15.1%	4.386	0.112
Nausea and vomiting	0	0.0%	0	0.0%	0	0.0%	0.000	1.000
Diarrhea	1	1.9%	2	3.8%	1	1.9%	0.513	0.774
Blue or green colored stool	0	0.0%	0	0.0%	0	0.0%	0.000	1.000
Dark stool containing blood	0	0.0%	0	0.0%	1	1.9%	2.013	0.366
Headache	8	15.1%	6	11.3%	13	24.5%	3.480	0.176
Dizziness	1	1.9%	2	3.8%	0	0.0%	2.038	0.361
Fatigue	11B	20.8%	10B	18.9%	20A	37.7%	5.981	0.049*
Fever	0	0.0%	0	0.0%	0	0.0%	0.000	1.000
Aching muscles	11	20.8%	4	7.5%	12	22.6%	5.086	0.079
Extreme thirst	0	0.0%	0	0.0%	0	0.0%	0.000	1.000
Tachycardia	0	0.0%	0	0.0%	4	7.5%	8.206	0.017*
Change in taste	0	0.0%	0	0.0%	0	0.0%	0.000	1.000
Sudden change in mood	4	7.5%	1	1.9%	5	9.4%	2.774	0.250
Depression	3	5.7%	3	5.7%	5	9.4%	0.781	0.677
Irritability	0	0.0%	0	0.0%	2	3.8%	4.051	0.132
Difficulty focusing	2	3.8%	3	5.7%	5	9.4%	1.494	0.474

Data are expressed number (%) Using: x2: Chi-square test and Fisher's Exact test p-value>0.05 is insignificant;
*p-value <0.05 is significant.

Also, there was no reported cases of kidney, heart, liver and brain damage in all groups during the study duration (p=1.000). This indicates that there was no association between CuT380A IUD and organ failure (Table 4).

Table (4): Comparison between groups according to organ failure.

	Organ failure	Group A (n=53)		Group B (n=53)		Group C (n=53)		x^2	p-value
		No.	%	No.	%	No.	%		
Kidney failure	Negative	53	100.0%	53	100.0%	53	100.0%	0.00	1.000
	Positive	0	0.0%	0	0.0%	0	0.0%		
Heart failure	Negative	53	100.0%	53	100.0%	53	100.0%	0.00	1.000
	Positive	0	0.0%	0	0.0%	0	0.0%		
Liver failure	Negative	53	100.0%	53	100.0%	53	100.0%	0.00	1.000
	Positive	0	0.0%	0	0.0%	0	0.0%		
Brain damage	Negative	53	100.0%	53	100.0%	53	100.0%	0.00	1.000
	Positive	0	0.0%	0	0.0%	0	0.0%		

Data are expressed number (%) Using: x2: Chi-square test and Fisher's Exact test, p-value>0.05 is insignificant

However, this was not confirmed by histological examination of the tissues of these organs as it was not feasible for living women. Finally, we found that the mean cu level was108.46 ± 22.93 for group A, followed by 104.13 ± 22.44 for group B, and 109.15 ± 22.66 for group C (with $p > 0.05$). This indicates that there was no association between CuT380A IUD and change of Cu (µg /dl) (Table 5**)**.

Table (5): Comparison between groups according to Cu (mcg/dl).

Cu (mcg/dl)	Group A (n=53)	Group B (n=53)	Group C (n=53)	F-test	P-value
Mean ± SD	108.46±22.93	104.13±22.44	109.15±22.66	0.762	0.469

Data are expressed as Mean ± SD, Using: F-One way Analysis of Variance test, p-value>0.05 is insignificant.

DISCUSSION

Recently, there has been a lot of interest in the subject of copper ion toxicity, especially in relation to the body's chronic systemic exposure [(6)].

Our study concluded higher frequency for fatigue and tachycardia in group C (non IUD users) than in groups A & B (with p-value < 0.05), while there was no statistically significant difference between groups according to the rest of general symptoms ($p > 0.05$), this indicates that the no association between CuT380A IUD and general symptoms. Our study found that there was no reported cases of kidney, heart, liver and brain damage in all groups during the study duration (p=1.000). This indicates that there was no association between CuT380A IUD and organ failure.

Copper poisoning is a rare condition that is mostly linked to hereditary disorders like Wilson disease that disrupt the balance of copper in the body. Wilson disease impairs the metabolism of copper and is an autosomal recessive genetic condition. According to research by **Liu *et al.*** [(7)]**,** a mutation in the ATP7B gene, which regulates ceruloplasmin production and copper excretion, causes an abnormal buildup of copper in key organs including the liver and brain. **Crandell and Mohler** [(8)] also state that common clinical manifestations of copper toxicity that can result from Wilson disease or other causes include gastrointestinal symptoms, renal failure, neurological issues, hepatic impairment, decreased bone density, cardiovascular issues, coma, and death.

In contrast to those who did not use the TCu380-A IUD, **Arnal *et al.*** [(9)] studied the levels of copper, ceruloplasmin, various markers of oxidative stress, and liver enzymes in those who used the IUD. Individuals who utilised IUDs showed higher levels of ceruloplasmin and plasma copper than the control group. This result is in agreement with our results. In the same line with our study, **More *et al.*** [(10)] found no discernible changes in plasma copper levels prior to, during, or following IUD usage. They carried out the first study on the concentration of copper in the blood of women using Cu lUDs. All participants had blood drawn at different times before to the IUD being installed, and again three, six, and twelve months after insertion. Furthermore, during the first two cycles after the IUD was removed, blood samples were obtained. They also performed a study of the Cu content in the devices one year before to and following implantation. The average yearly emission of the devices, according to the study, was 10 mg, translating into an average daily emission of 28.7 mg [(10)].

Women who used copper IUDs, non-cu IUDs, and oral contraceptives had their blood copper and serum ceruloplasmin levels measured by **Conforti *et al.*** [(11)]. Serum levels of ceruloplasmin and copper were the same in both IUD-using groups, but they were surprisingly higher in the oral contraceptive pill (COC) groups than in the IUD groups. However, the baseline serum copper levels were not measured prior to the implantation of the lUDs in order to make a comparison.

In a research on serum copper levels, **Rubin *et al.*** [(12)] divided the participants into three groups: Those who used no contraception at all, those who used an IUD that wasn't made of copper, and those who used a copper IUD for no more than 48 months. In all investigations, there were only slight differences in the serum copper levels between the groups when the length of consumption was taken into account. The researchers also measured the 24-hour urine copper excretion, which was found to be consistent in a number of groups. Accordingly, the authors proposed that copper from IUDs is neither excreted in urine nor absorbed into the circulation. Since there aren't many

human researches examining the amounts of copper in tissues, they were unable to completely rule out the idea that tissues store copper [12]. Also, in contrast to both non-Cu IUD users and control groups, **Grillo *et al.*** [13] found no statistically significant increases in serum copper levels among those who used Cu IUDs.

Our study is in agreement with **Bo *et al.*** [14] who looked at the copper levels in women who used copper IUDs, levonorgestrel IUDs, and oral contraceptives, as well as a control group of women who did not use contraception. When compared to the control and IUD groups, the mean plasma copper level of COC users was found to be significantly higher. Between the two IUD-using groups, there was no statistically significant difference in blood copper levels. The results of this investigation confirmed that those who use Cu IUDs do not have higher copper concentrations. The most recent study was carried out by **Fan *et al.*** [15] where participants' blood copper and zinc levels were compared three months before to and following the implantation of a Cu IUD. Neither metal's concentration increased much. Their findings appear to confirm that copper IUDs are safe [15]. Our study found that this wasn't confirmed by histological examination of the tissues of these organs as it wasn't feasible for living women. Finally, we found that that the mean cu level was108.46 ± 22.93 for group A; followed by 104.13 ± 22.44 for group B and 109.15 ± 22.66 for group C, with $p > 0.05$. This indicates that there was no association between CuT380A IUD and change of Cu (µg /dl).

Studies evaluating the degree of tissue damage in the organs of women wearing copper LUDs are currently few. Using a rat model, **Zhao *et al.*** [5] evaluated the systemic toxicity of copper in this study. For a period of 26 weeks, or around 15 to 17 human years, female Wistar rats had copper IUDs surgically inserted into their uterine horns. The authors' conclusions include that within the designated time, all of the rats showed normal body weight and development. The authors removed and examined the animals' brains, hearts, livers, spleens, lungs, kidneys, and adrenal glands after the 26-week period. The organ coefficient, a measure of toxicity, did not show any discernible differences between the copper groups and the control group. Histologic and pathologic investigation revealed no obvious structural damage or abnormalities of the organs in any of the groups [16].

Limitations: It is critical to acknowledge the limitations of the study. In comparison with the study's findings, there were fewer instances and a smaller sample size because it was carried out in a hospital. The study did not represent a specific community and there was a considerable danger of publication bias due to its lack of multicentricity.

CONCLUSIONS

According to our findings, there was no rise in blood copper levels among IUD users, regardless of duration of use. The Copper T380A IUD may be used safely without danger of Cu toxicity. The current study could add to existing information and give insight on future prospective studies with bigger sample numbers and longer durations of follow-up to review our findings.

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