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# Evaluation of some trace elements status in females type 1 diabetics patients and its relationship with oxidative stress

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ABSTRACT

Disorders of trace elements in diabetic patients with type 1 are possibly led to glucose metabolism disturbance and increased oxidation, which may promote the development of diabetes and insulin resisting. We aim to clarify the role of the serum level of zinc (Zn), copper (Cu), cobalt (Co), iron (Fe), Zn/Cu ratio and their relations with the degree of oxidative stress in females T1D. The study included 35 healthy women and 54 women with insulin-dependent diabetes Serum levels of trace element have determined by atomic absorption spectrophotometer. Results showed a decrease levels of Cu, Fe, Zn and MDA in diabetes patients compared to controls (p <0.000), (p < 0.000) (p< 0.001) (p <0.001) correspondingly. Significance in correlations amid Zn and age (r= -0.449, p <0.032), significance in correlations among Co in addition to age (r= -0.434, p <0.038) with significances in correlation amid Fe and MDA (r= 0.024, p <0.366).

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## INTRODUCTION

Diabetes (DM) includes a range of metabolic disorders that diagnose massive levels of glucose in the blood. A series of health problems threaten people with diabetes that lead to higher medical care requirements and an increased mortality rate (Baena-Díez *et al.*, 2016). Extraordinary blood sugar levels consistently result in general damage to the blood vessels and affect the nerves, kidneys, eyes, and heart that lead to various complications (Organization, 2009). The dominance of diabetes for aged adults from 18 to 99 years was estimated at 8.4% in 2017, which could rise to 9.9% in 2045 (Cho *et al.*, 2018). Type 1 diabetes (T1D) has been known to be a metabolic disorder with autoimmune immunity that selects insulin produced $\beta$ cells in the pancreas. It accounts for 5-10% of people with diabetes, often with the term insulin-dependent diabetes.

The developed diabetic complications can be linked to augmented oxidative stress in DM. Increased oxidative stress in diabetes means an increased oxidative/nitrosative stress and consider as a significant pathway in the complications of diabetes (Rojas and Tegeder, 2018). Malondialdehyde (MDA) stands for a steady end consequence of lipid peroxidation. The increment of MDA levels in plasma and various tissues has testified in diabetic patients (Moussa, 2008; Bandeira *et al.*, 2012).

Trace elements have been reported as key co factors of anti-inflammation and antioxidant system. SO, in the body, the trace elements must be present in proper levels (Liu *et al.*, 2018; Ozturk *et al.*, 2013).

Previous studies have demonstrated abnormal statues of trace elements in diabetic patients (Siddiqui *et al.*, 2014; Wolide *et al.*, 2017). Trace elements like Zn, Se, Cr, Mg, and other have essential functions in cellular homeostasis and body metabolism (Ferreira and Gahl, 2017). This consists of creation, emission and insulin activity passageway (Ahmed *et al.*, 2018; Sun *et al.*, 2018; Triggiani, 2006). Increase insulin sensitivity and acts as an antioxidant that prevents tissue for each oxidation, helping as a co factor for enzyme systems that participating in glucose metabolic rate (Akinloye *et al.*, 2010).

Significant variations in some levels of trace elements occur owing to chronic hyperglycemia. Most papers have demonstrated the relationship of trace elements with type 2 diabetes (Atalay *et al.*, 2017; Alwan, 2017; Sanjeevi and Freeland-Graves, 2018). Based on above, it is necessary to assess the vital element levels in type1 diabetic and the current study, we focus on some trace element in female patients of diabetes type1 and to investigate its association with oxidative stress. Disorder in trace element levels and augmented oxidative stress in diabetic Mellitus has a role in the growth of diabetic complication (Vincent *et al.*, 2004). The present paper has carried out to guess the serum levels of Cu, Zn, Co, Fe besides Zn/Cu patients with their relationship with Malondialdehyde.

Trace elements can affect in various ways the beginning or pathogenesis of diabetes. Initial disproportions of particular trace elements can distract typical glucose and insulin metabolic rate, or possibly will result in augmented oxidative stress that motivates insulin resisting and the expansion of diabetes complications (Rojas and Tegeder, 2018). Numerous research articles have depicted that Cu causes oxidative stress and stands for a pro-oxidant and might contribute to metal-catalyzed creation of free radicals. Copper act as an influential enzyme catalyst and a hazardous reactant which produces hydroxyl radical (Kratz and Ferraro, 2004). The lack of Cu causes decreased insulin response, glucose intolerance and increased glucose response (Viktorinova and Tošerová, 2009). The cobalt performance results in raised glucose expression of transporter 1 (GLUT1) with inhibited gluconeogenesis in diabetic rats (Saker *et al.*, 1998).

Cobalt only or with a grouped ascorbate drops lipid peroxidation in diabetic rats in several organs like kidney, liver, aorta and heart (Yildirim and Büyük-bingöl, 2003).

Zinc stands for the $2^{nd}$ highly abundant trace element in the humanoid body after Fe. The zinc transfer to beta cells in the pancreas is necessary for producing insulin and its active packaging in the vesicles. It is correspondingly an incorporated portion of insulin and directly concerned in the production, storing and emission of insulin. It is necessary as a cofactor for numerous involved enzymes in glucose metabolic rate with an integral constituent of some antioxidant enzymes (Zinc, 2005; Wijesekara *et al.*, 2009).

Iron was anticipated to impact the diabetes development by numerous mechanisms, particularly initiation of insulin shortage and insulin resisting in addition to instigating hepatic dysfunction (Simcox and McClain, 2013).

## MATERIALS AND METHODS

A clinical investigation has accomplished in Al-Najaf Center for Diabetes and Endocrinology (Al-Najaf City, Iraq). All blood samples of patients were collected in fasting state (8-10 hr)

From 8 p.m. until 8 a.m., about 10 ml of blood has been drawn from the capital vein for every participant by means of a sterilized one-use plastic syringe. The tester has left to clot, and the serum has been separated as a result of centrifugation.

The study population has allocated into dual groups (Gr-I and Gr-II). Gr-I non-diabetic individuals as control groups, Group II has females Type-1 Diabetic Patients.

The diabetic group has 54 patients, who chosen from Type-1 Diabetic Patients, the control group has 35 seemingly healthy subjects who have been selected the same centre workers.

The medical history of each patient was taken, which included family history, type of treatment, duration of disease, and history of any other illness have on the patients who have essential in this study. Measurements of length and weight were done to calculate body mass index

Exclusion principles contain antenatal women, lactating mothers, Smokers, along with alcoholic persons. Everyone on medication, which might influence the contact to measured metals-women with another chronic disease, has been likewise left out.

Glucose measurement is based on the PAP enzymatic determination of glucose by using the RanDox kit. Investigation of trace elements by means of Atomic Absorption Spectrophotometric technique (AA6300 Shimadzo Company). Serum MDA has

recorded using the thiobarbituric acid (TBA) reaction (Muslih, 2002).

## Statistical

Intended for inter group evaluation, the typically distributed variables have been compared utilizing independent samples t-test. Correlations between numeric data were expressed as Pearson's correlation co-efficients. The significant statistical level was considered at $P < 0.05$.

## RESULTS AND DISCUSSION

The patient group included two groups (G1, G2). Group 1(control group) consists of 35 women, group 2 (type 1 diabetes) comprised 54 women. The medical and biological features of the patients and controls have been presented in Tables 1, 2, 3, 4, 5, 6, 7 and 8.

**Table 1: Clinical features for patients**

| Group | Healthy subjects | Diabetic Patients type 1 Females |
|---|---|---|
| Number | 35 | 54 |
| Age (yrs) | 42.83± 12.23 | 52.12 ±14.68 |
| BMI (kg/m$^2$) | 26.6 ± 1.6 | 27.65 ± 4.49 |
| FBS (mg/dl) | 85.80 ± 13.83 | 265.48± 86.1 |

Diabetes stands for a global health care disaster that necessitates innovative methodologies for deterrence and treatment. Diabetes was connected with anomalies in the metabolic rate of Cu, Zn, Fe. Besides, the deficiency of these metals was testified as annoying influences in the illness expansion (Walter et al., 1991; Fujimoto, 1987).

Many trace elements have been imperative for humanoid metabolic operation. Frequent researches have validated the essential parts of trace element as zinc, chromium, selenium, magnesium, molybdenum, vanadium and copper in insulin performance in addition to metabolic carbohydrate rate (Wiernsperger and Rapin, 2010). The real role of these trace elements in the progression, while pathogenesis of diabetes is up to date indistinct (Tuvemo, 1983). The experimental variations in the significance of these features in people with diabetes were based on hyperglycemia and augmented protein glycosylation in this circumstance (Zheng et al., 2008).

Many studies reported that trace elements were linked to diabetes and its complications (Simcox and McClain, 2013; Kruse-Jarres and Rükgauer, 2000; Zheng et al., 2008; Kazi et al., 2008; Flores et al., 2011). This research work has shown that serum Fe, Cu, and Zn levels have been significantly lower in women with T1DM when compared with healthy controls.

## Iron

It stands for a necessary nutrient and a prospective toxicant to cells. The providing of adequate Fe quantities is required for the process of numerous biological procedures, involving oxygen binding and conveyance, electron transmission reacting, ruling cell growing and differentiation, regulating cell growth, is likewise involved in the appropriate function of the immune system and gene regulating (Siddiqui et al., 2014; Hershko et al., 1988).

Furthermore, iron supplementation should be a potential target therapy for patients at risk for T2DM (Walter et al., 1991). In our research work, the serum iron level is decreased in the patient group compared with control. This consequence is agreed with (Atalay et al., 2017), but they are inconsistent with (Montonen et al., 2012). In previous studies, serum iron and ferritin levels were correlated with glucose concentration, insulin and related to poor glycemic control in the patients with T2DM (Fernández-Real et al., 2004; Canturk, 2003) in another study iron linked with triglycerides and were undesirably correlated with BMI and CRP (Atalay et al., 2017). Iron levels in our study were significantly associated with MDA Table 8.

## Copper

Copper stands for an influential enzyme catalyst and a risky reactant that produces hydroxyl radical. Cu shortage causes augmented glucose reaction, glucose intolerance and reduced insulin response. It is related to hypercholesterolemia and atherosclerosis. Cu owns an insulin-like activity with supported lipogenesis (Kazi et al., 2008; Ekmekcioglu et al., 2001).

It is as well another trace element that is primarily needed for the activity of superoxide dismutase (SOD) and cytochrome oxidase (Khan, 2014). However, the data about Cu and its effect on glucose metabolism or the way its deficiency influences diabetes is limited in the literature. Few papers described that male patients with diabetes had increased serum Cu levels, but female patients had normal levels (Walter et al., 1991; Noto et al., 1984). Reported that serum Cu levels ranged from normal in diabetics (Pidduck, 1970). Our results demonstrated that women with diabetes had significantly lower plasma Cu levels than healthy women.

**Table 2: Levels of Cu (mg/l) in control group and insulin-dependent diabetes**

| Metal | Group | Mean | Std. Deviation | Std. Error | 95% Confidence Interval of the Difference | | sign |
|-------|-------|------|----------------|------------|------------|------------|------|
| | | | | | Lower | Upper | |
| cu | 1.00 | 1.94 | 0.948 | 0.143 | 0.411 | 1.047 | 0.000 |
| | 2.00 | 1.21 | 0.476 | 0.071 | 0.409 | 1.049 | |

**Table 3: Levels of Fe (mg/l) in control group and insulin-dependent diabetes**

| Metal | Group | Mean | Std. Deviation | Std. Error | 95% Confidence Interval of the Difference | | sign |
|-------|-------|------|----------------|------------|------------|------------|------|
| | | | | | Lower | Upper | |
| Fe | 1.00 | 66.47 | 7.738 | 1.166 | 28.164 | 35.03 | 0.000 |
| | 2.00 | 34.87 | 8.446 | 1.273 | 28.16 | 35.03 | |

**Table 4: Levels of Co (mg/l) in control group and insulin-dependent diabetes**

| Metal | Group | Mean | Std. Deviation | Std. Error | 95% Confidence Interval of the Difference | | sign |
|-------|-------|------|----------------|------------|------------|------------|------|
| | | | | | Lower | Upper | |
| co | 1.00 | 2.80 | 0.745 | 0.112 | 0.034 | 0.821 | 0.069 |
| | 2.00 | 2.37 | 1.079 | 0.162 | 0.033 | 0.821 | |

**Table 5: Levels of Zn(mg/l) in control group and insulin-dependent diabetes**

| Metal | Group | Mean | Std. Deviation | Std. Error | 95% Confidence Interval of the Difference | | sign |
|-------|-------|------|----------------|------------|------------|------------|------|
| | | | | | Lower | Upper | |
| zn | 1.00 | 5.70 | 4.36 | 0. 89 | 1.324 | 4.608 | 0.001 |
| | 2.00 | 2.74 | 0.99 | 0.149 | 1.128 | 4.804 | |

**Table 6: Levels of ratio (mg/l) in control group and insulin-dependent diabetes**

| Metal | Group | Mean | Std. Deviation | Std. Error | 95% Confidence Interval of the Difference | | sign |
|-------|-------|------|----------------|------------|------------|------------|------|
| | | | | | Lower | Upper | |
| Zn/cu | 1.00 | 3.72 | 2.094 | 0.84 | -.288 | 2.834 | .109 |
| | 2.00 | 2.45 | 0.981 | 0.147 | -.473 | 3.019 | |

**Table 7: Levels of MDA($\mu$mol/l)in the control group and insulin-dependent diabetes**

| MDA | Group | Mean | Std. Deviation | Std. Error | 95% Confidence Interval of the Difference | | sign |
|---|---|---|---|---|---|---|---|
| | | | | | Lower | Upper | |
| | 1.00 | 5.05 | 2.893 | 1.076 | -17.204- | -6.411 | |
| | 2.00 | 7.97 | 5.829 | 2.243 | -16.799- | -6.815 | |

**Table 8: Correlation analyses between selected trace element and FBG, AGE, BMI, DUR in female type 1 diabetes**

| Measured Parameter | | MDA | FBS | AGE | BMI | DUR |
|---|---|---|---|---|---|---|
| CU | r value | 0.010 | -0.057 | -0.255 | -0.041 | 0.000 |
| | P value | 0.951 | 0.796 | 0.239 | 0.852 | 0.999 |
| FE | r value | 0.366* | -0.100 | 0.026 | 0.077 | 0.278 |
| | P value | 0.024 | 0.651 | 0.906 | 0.726 | 0.200 |
| CO | r value | -0.122- | 0.205 | -0.434* | -0.286 | 0.086 |
| | P value | 0.465 | 0.347 | 0.038 | 0.186 | 0.697 |
| ZN | r value | 0.008 | -0.069 | -0.449* | -0.142 | -0.225 |
| | P value | 0.962 | 0.756 | 0.032 | 0.517 | 0.302 |
| Ratio | r value | 0.095 | -0.045 | -0.022 | 0.067 | -0.077 |
| | P value | 0.572 | 0.839 | 0.921 | 0.760 | 0.726 |

*Correlation is insignificance at0.05 level (2-tailed)

Low plasma Cu levels may induce diabetes by resulting in oxidative stress. Previous studies have shown inconsistent fallouts with regard to Cu status in diabetes patients. E.g., reduction or no alteration in Cu levels has been stated in (Leonhardt *et al.*, 1996; Rohn *et al.*, 1993) and no statistical difference existed in Copper level in diabetic and healthful patients (Kazi *et al.*, 2008; Ekmekcioglu *et al.*, 2001) whereas increased plasma Cu levels as stated in (Ahmed *et al.*, 2018; Qiu *et al.*, 2017; Lowe and da Silva, 2017). No significant correlation between copper and FBS, AGE, BMI, DUR(duration).

Cu/Zn-SODs, Cu concentration in the human body, is an essential indicator of health. Changes in plasma levels of Cu and the imbalanced ratio of Cu/Zn have been demonstrated to be indicators of infection, vascular barriers, and other illnesses (Barrera *et al.*, 2003). In the current study, no significant between-the group in the serum ratio (Zn/Cu) These results conflict with (Baena-Díez *et al.*, 2016). No correlation between ratio and FBS, AGE, BMI, DUR

**Zinc**

Zinc has a significant role in glucose metabolic rate (Isbir *et al.*, 1994). Zinc can contribute to the control of insulin receptor-initiated signal transudation process in addition to insulin receptor creation (Tang and Shay, 2001). It supports the use of glucose by muscle and fat cells. It requires to be a cofactor for the operation of intracellular enzymes that can be in glucose metabolic rate, protein as well as lipid. The reduction in Zn can potentiate the poisonousness of other metals like copper and iron. Zinc shortages in people with diabetes are linked with other free-radical action and the augmented lipids oxidation, breaking the arteries, heart, and other essential portions of the vascular

system. Zinc shortage damages their creation, causing raised oxidative stress (Kelly, 1998). The antigenic features of zinc influence binding of insulin to hepatocyte membranes and a shortage possibly will cause augmented insulin confrontation and hyperglycemia. Lower zinc levels have similarly been realized to produce reduced or slowed wound healing, that is usual in diabetic patients (Watts, 2003). Oxidative stress has a significant part in the diabetes pathogenesis and its complications. Medical researches stated that serum levels of zinc are typically smaller in T2D patients than nondiabetic as a result of the reduced intestinal absorption of endogenous zinc and the intensification in zinc excretion into the intestine throughout digestive processing can cause this near to the ground serum zinc level (Salgueiro and Krebs, 2001). In our study, we observed decreases in zinc levels. These results correspond to previous results. We found a significant correlation between zinc and age.

### Cobalt

While we collected sources of trace elements with diabetes, we found few studies on diabetes (Siddiqui et al., 2014; Abdullah and Salh, 2017). These studies showed cobalt deficiency with type 2 diabetes. Our results showed no change in cobalt levels between groups, and significantly correlated with age.

### CONCLUSION

The serum level role of Zn, Cu, Co, Fe, Zn/Cu ratio and their relations with the degree of oxidative stress in females T1D has been investigated. The study has been conducted with 35 healthy women and 54 women with insulin-dependent diabetes Serum levels of trace element have concluded through atomic absorption spectrophotometer. Accordingly, there is decreased levels of Cu, Fe, Zn and MDA in diabetes patients compared to controls ($p < 0.000$), ($p < 0.000$) ($p < 0.001$) and ($p < 0.001$) respectively. Significance in correlations amid Zn and age (r= -0.449, $p < 0.032$), significance in correlations among Co in addition to age (r= -0.434, $p < 0.038$) with significances in correlation amid Fe and MDA (r= 0.024, $p < 0.366$). Also, there is no variation in cobalt levels among groups, while it is significantly correlated with age.

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