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

# Seenaa kadhum Ali\*1, Elham Abed Mahdi1, Zinah Kadhim Kareem2, Mohanad Kadhim Ali3, Ayad Kadhim Ali4

1Department of Chemistry, Faculty of Education for Women, Kufa University, Najaf, Iraq

2Mustansiriyah University, Baghdad, Iraq

3Iraqi Ministry of Health , The Najaf Health Directorate, Baghdad, Iraq

4Department of Soil Science and Water, Faculty of Agriculture, Kufa University, Najaf , Iraq



Abstract

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Disorders of trace elements in diabetic patients with type 1 are possibly led to glucose metabolism disturbance and increased oxidation, which may pro- mote 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).

\*Corresponding Author

Name: Seenaa kadhum Ali Phone:

Email: [seenaa.alhusseini@uokufa.edu.iq](mailto:seenaa.alhusseini@uokufa.edu.iq)

to the blood vessels and affect the nerves, kid- neys, eyes, and heart that lead to various compli- cations ([Organization](#_bookmark28), [2009](#_bookmark28)). The dominance of diabetes for aged adults from 18 to 99 years was

estimated at 8.4% in 2017, which could rise to

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## INTRODUCTION

Diabetes (DM) includes a range of metabolic dis- orders that diagnose massive levels of glucose in the blood. A series of health problems threaten people with diabetes that lead to higher medi- cal care requirements and an increased mortality rate ([Baena-Díez *et al.*](#_bookmark8), [2016](#_bookmark8)). Extraordinary blood sugar levels consistently result in general damage

9.9% in 2045 ([Cho *et al.*](#_bookmark15), [2018](#_bookmark15)). Type 1 diabetes (T1D) has been known to be a metabolic disorder with autoimmune immunity that selects insulin pro- duced *β* 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 dia- betes ([Rojas and Tegeder](#_bookmark36), [2018](#_bookmark36)). 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](#_bookmark22), [2008](#_bookmark22); [Bandeira *et al.*](#_bookmark13), [2012](#_bookmark13)).

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.*](#_bookmark41), [2018](#_bookmark41); [Ozturk *et al.*](#_bookmark30), [2013](#_bookmark30)).

Previous studies have demonstrated abnormal stat- ues of trace elements in diabetic patients ([Siddiqui](#_bookmark45) [*et al.*](#_bookmark45), [2014](#_bookmark45); [Wolide *et al.*](#_bookmark61), [2017](#_bookmark61)). Trace elements like Zn, Se, Cr, Mg, and other have essential functions in cellular homeostasis and body metabolism ([Ferreira](#_bookmark19) [and Gahl](#_bookmark19), [2017](#_bookmark19)). This consists of creation, emis- sion and insulin activity passageway ([Ahmed *et al.*](#_bookmark9), [2018](#_bookmark9); [Sun *et al.*](#_bookmark49), [2018](#_bookmark49); [Triggiani](#_bookmark53), [2006](#_bookmark53)). 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 glu- cose metabolic rate ([Akinloye *et al.*](#_bookmark10), [2010](#_bookmark10)).

Significant variations in some levels of trace ele- ments occur owing to chronic hyperglycemia. Most papers have demonstrated the relationship of trace elements with type 2 diabetes ([Atalay *et al.*](#_bookmark11), [2017](#_bookmark11); [Alwan](#_bookmark12), [2017](#_bookmark12); [Sanjeevi and Freeland-Graves](#_bookmark43), [2018](#_bookmark43)). Based on above, it is necessary to assess the vital ele- ment 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 lev- els and augmented oxidative stress in diabetic Mel- litus has a role in the growth of diabetic complica- tion ([Vincent *et al.*](#_bookmark56), [2004](#_bookmark56)). 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 begin- ning or pathogenesis of diabetes. Initial dispropor- tions of particular trace elements can distract typ- ical glucose and insulin metabolic rate, or possi- bly will result in augmented oxidative stress that motivates insulin resisting and the expansion of diabetes complications ([Rojas and Tegeder](#_bookmark36), [2018](#_bookmark36)). 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](#_bookmark35), [2004](#_bookmark35)). The lack of Cu causes decreased insulin response, glucose intolerance and increased glucose response ([Vik-](#_bookmark55) [torinova and Tošerová](#_bookmark55), [2009](#_bookmark55)). The cobalt perfor- mance results in raised glucose expression of trans- porter 1 (GLUT1) with inhibited gluconeogenesis in diabetic rats ([Saker *et al.*](#_bookmark39), [1998](#_bookmark39)).

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-](#_bookmark47)

[bingöl](#_bookmark47), [2003](#_bookmark47)).

Zinc stands for the 2*nd* highly abundant trace ele- ment in the humanoid body after Fe. The zinc trans- fer to beta cells in the pancreas is necessary for pro- ducing insulin and its active packaging in the vesi- cles. 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](#_bookmark51), [2005](#_bookmark51); [Wijesekara *et al.*](#_bookmark60), [2009](#_bookmark60)).

Iron was anticipated to impact the diabetes develop- ment by numerous mechanisms, particularly initia- tion of insulin shortage and insulin resisting in addi- tion to instigating hepatic dysfunction ([Simcox and](#_bookmark48) [McClain](#_bookmark48), [2013](#_bookmark48)).

## 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 col- lected 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 partici- pant 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 con- trol 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. Mea- surements of length and weight were done to calcu- late body mass index

Exclusion principles contain antenatal women, lac- tating mothers, Smokers, along with alcoholic per- sons. Everyone on medication, which might influ- ence the contact to measured metals-women with another chronic disease, has been likewise left out.

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

recorded using the thiobarbituric acid (TBA) reac- tion ([Muslih](#_bookmark23), [2002](#_bookmark23)).

## 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 corre- lation 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 med- ical and biological features of the patients and con- trols have been presented in Tables [1](#_bookmark0), [2](#_bookmark1), [3](#_bookmark2), [4](#_bookmark3), [5](#_bookmark4), [6](#_bookmark5), [7](#_bookmark6)

and [8](#_bookmark7).

## Table 1: Clinical features for patients

[McClain](#_bookmark48), [2013](#_bookmark48); [Kruse-Jarres and Rükgauer](#_bookmark37), [2000](#_bookmark37); [Zheng *et al.*](#_bookmark50), [2008](#_bookmark50); [Kazi *et al.*](#_bookmark29), [2008](#_bookmark29); [Flores *et al.*](#_bookmark20), [2011](#_bookmark20)). 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 quan- tities is required for the process of numerous biolog- ical procedures, involving oxygen binding and con- veyance, 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](#_bookmark45) [*et al.*](#_bookmark45), [2014](#_bookmark45); [Hershko *et al.*](#_bookmark25), [1988](#_bookmark25)).

Furthermore, iron supplementation should be a potential target therapy for patients at risk for T2DM ([Walter *et al.*](#_bookmark57), [1991](#_bookmark57)). In our research work,

Group Healthy sub- jects

Diabetic Patients type 1

Females

the serum iron level is decreased in the patient group compared with control. This consequence is agreed with ([Atalay *et al.*](#_bookmark11), [2017](#_bookmark11)), but they are

Number 35 54

Age (yrs) 42.83*±* 12.23 52.12 *±*14.68

inconsistent with ([Montonen *et al.*](#_bookmark46), [2012](#_bookmark46)). In pre- vious studies, serum iron and ferritin levels were

BMI

(kg/m2) FBS

(mg/dl)

26.6 *±* 1.6 27.65 *±* 4.49

85.80 *±* 13.83 265.48*±* 86.1

correlated with glucose concentration, insulin and related to poor glycemic control in the patients with T2DM ([Fernández-Real *et al.*](#_bookmark18), [2004](#_bookmark18); [Canturk](#_bookmark16), [2003](#_bookmark16)) in another study iron linked with triglycerides and were undesirably correlated with BMI and CRP ([Ata-](#_bookmark11) [lay *et al.*](#_bookmark11), [2017](#_bookmark11)). Iron levels in our study were signif-

Diabetes stands for a global health care disas- ter 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 ([Wal-](#_bookmark57) [ter *et al.*](#_bookmark57), [1991](#_bookmark57); [Fujimoto](#_bookmark24), [1987](#_bookmark24)).

Many trace elements have been imperative for humanoid metabolic operation. Frequent researches have validated the essential parts of trace element as zinc, chromium, selenium, mag- nesium, molybdenum, vanadium and copper in insulin performance in addition to metabolic car- bohydrate rate ([Wiernsperger and Rapin](#_bookmark59), [2010](#_bookmark59)). The real role of these trace elements in the pro- gression, while pathogenesis of diabetes is up to date indistinct ([Tuvemo](#_bookmark54), [1983](#_bookmark54)). The experimental variations in the significance of these features in people with diabetes were based on hyper- glycemia and augmented protein glycosylation in this circumstance ([Zheng *et al.*](#_bookmark50), [2008](#_bookmark50)).

Many studies reported that trace elements were linked to diabetes and its complications ([Simcox and](#_bookmark48)

icantly associated with MDA Table [8](#_bookmark7).

## Copper

Copper stands for an influential enzyme catalyst and a risky reactant that produces hydroxyl radical. Cu shortage causes augmented glucose reaction, glu- cose intolerance and reduced insulin response. It is related to hypercholesterolemia and atherosclero- sis. Cu owns an insulin-like activity with supported lipogenesis ([Kazi *et al.*](#_bookmark29), [2008](#_bookmark29); [Ekmekcioglu *et al.*](#_bookmark17), [2001](#_bookmark17)).

It is as well another trace element that is primar- ily needed for the activity of superoxide dismu- tase (SOD) and cytochrome oxidase ([Khan](#_bookmark33), [2014](#_bookmark33)). However, the data about Cu and its effect on glu- cose metabolism or the way its deficiency influ- ences 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.*](#_bookmark57), [1991](#_bookmark57); [Noto *et al.*](#_bookmark26), [1984](#_bookmark26)). Reported that serum Cu levels ranged from normal in diabetics ([Pidduck](#_bookmark31), [1970](#_bookmark31)). Our results demonstrated that women with diabetes had signif- icantly 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 | sign |
|  |  |  |  |  | Difference |  |
|  |  |  |  |  | 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 | sign |
|  |  |  |  | Difference |  |
|  |  |  |  | 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 | sign |
|  |  |  |  | Difference |  |
|  |  |  |  | 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 | sign |
|  |  |  |  |  | Difference |  |
|  |  |  |  |  | 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 | sign |
|  |  |  |  | Difference |  |
|  |  |  |  | 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(*µ*mol/l)in the control group and insulin-dependent diabetes**

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

**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 result- ing 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.*](#_bookmark40), [1996](#_bookmark40); [Rohn *et al.*](#_bookmark38), [1993](#_bookmark38)) and no statistical differ- ence existed in Copper level in diabetic and health- ful patients ([Kazi *et al.*](#_bookmark29), [2008](#_bookmark29); [Ekmekcioglu *et al.*](#_bookmark17), [2001](#_bookmark17)) whereas increased plasma Cu levels as stated in ([Ahmed *et al.*](#_bookmark9), [2018](#_bookmark9); [Qiu *et al.*](#_bookmark34), [2017](#_bookmark34); [Lowe and](#_bookmark44) [da Silva](#_bookmark44), [2017](#_bookmark44)). 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, vas- cular barriers, and other illnesses ([Barrera *et al.*](#_bookmark14), [2003](#_bookmark14)). In the current study, no significant between-

the group in the serum ratio (Zn/Cu) These results conflict with ([Baena-Díez *et al.*](#_bookmark8), [2016](#_bookmark8)). No correla- tion between ratio and FBS, AGE, BMI, DUR

## Zinc

Zinc has a significant role in glucose metabolic rate ([Isbir *et al.*](#_bookmark27), [1994](#_bookmark27)). Zinc can contribute to the control of insulin receptor-initiated signal transu- dation process in addition to insulin receptor cre- ation ([Tang and Shay](#_bookmark52), [2001](#_bookmark52)). 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 potenti- ate 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, caus- ing raised oxidative stress ([Kelly](#_bookmark32), [1998](#_bookmark32)). The anti- genic features of zinc influence binding of insulin to hepatocyte membranes and a shortage possi- bly 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](#_bookmark58), [2003](#_bookmark58)). 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 nondia- betic as a result of the reduced intestinal absorp- tion of endogenous zinc and the intensification in zinc excretion into the intestine throughout diges- tive processing can cause this near to the ground serum zinc level ([Salgueiro and Krebs](#_bookmark42), [2001](#_bookmark42)). 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](#_bookmark45) [*et al.*](#_bookmark45), [2014](#_bookmark45); [Abdullah and Salh](#_bookmark21), [2017](#_bookmark21)). 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 oxida- tive stress in females T1D has been investigated. The study has been conducted with 35 healthy women and 54 women with insulin-dependent dia- betes Serum levels of trace element have con- cluded through atomic absorption spectrophotome- ter. 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.

## REFERENCES

Abdullah, A., Salh, D. 2017. Determination of serum zinc, manganese, copper and cobalt traces in type two diabetic patients in Sulaimaniyah city using icp technique. *Ibn AL-Haitham Journal For Pure and Applied Science*, 25(3):220–225.

Ahmed, A. M., Khabour, O., Awadalla, A. H. 2018. Serum trace elements in insulin-dependent and non-insulin-dependent diabetes: a comparative study. . *Diabetes, metabolic syndrome and obesity: targets and therapy*, 4:887–892.

Akinloye, O., Ogunleye, K., Oguntibeju, O. 2010. Cad- mium, lead, arsenic and selenium levels in patients with type 2 diabetes mellitus. *African Journal of Biotechnology*, 32(5189-95).

Alwan, I. F. 2017. *Hamood AM, editors. Serum trace elements in patients with Type 2 diabetes mellitus*.

Atalay, H., Boyuk, B., Guzel, S. 2017. Serum Trace Ele- ments in Type 2 Diabetes Mellitus. *Acta Medica*, 33(795):795–800.

Baena-Díez, J. M., Peñafiel, J., Subirana, I., Ramos, R., Elosua, R., Marín-Ibañez, A. 2016. Risk of cause- specific death in individuals with diabetes: a com- peting risks analysis. *Diabetes Care*, 11(1987-95).

Bandeira, M., Guedes, S., Fonseca, L. 2012. Charac- terization of blood oxidative stress in type 2 dia- betes mellitus patients: increase in lipid peroxida- tion and SOD activity. *Oxidative medicine and cel- lular longevity*, pages 1–14.

Barrera, R., Schattner, M., Gabovich, N., Zhang, J., Saeed, M., Genao, A. 2003. Bacteremic episodes and copper/zinc ratio in patients receiving home parenteral nutrition. *Nutrition in Clinical Practice*, 6(529-32).

Canturk, Z. 2003. Çetinarslan B, Tarkun İ, Zafer Can- turk N. Serum ferritin levels in poorly-and well- controlled diabetes mellitus. *Endocrine research*, 3(299-306).

Cho, N., Shaw, J., Karuranga, S. 2018. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes research and clinical practice*, 138:271–81.

Ekmekcioglu, C., Prohaska, C., Pomazal, K., Steffan, I. 2001. Schernthaner G, Marktl W. Concentrations of seven trace elements in different hematological matrices in patients with type 2 diabetes as com- pared to healthy controls. *Biological Trace Element Research*, 3(205-19).

Fernández-Real, J. M., López-Bermejo, A., Ricart, W. 2004. Cross talk between iron metabolism and diabetes. Annals of clinical biochemistry. *Perspec- tives in Diabetes*, 51(8):2348–2354.

Ferreira, C. R., Gahl, W. A. 2017. Disorders of metal metabolism. *Translational science of rare diseases*, 2(3-4):101–139.

Flores, C. R., Puga, M. P., Wrobel, K., Sevilla, M. E. G., Wrobel, K. 2011. Trace elements status in diabetes mellitus type 2: possible role of the interaction

between molybdenum and copper in the progress of typical complications. *Diabetes research and clinical practice*, 3(333-41).

Fujimoto, S. 1987. Studies on the relationships between blood trace metal concentrations and the clinical status of patients with cerebrovascu- lar disease, gastric cancer and diabetes mellitus. [Hokkaido igaku zasshi] The Hokkaido journal of medical. *science*, 6(913-32).

Hershko, C., Peto, T., Weatherall, D. 1988. Regular review: iron and infection. British medical journal. *(Clinical research ed)*, 1988(296).

Isbir, T., Taylor, A., Tamer, L. 1994. Zinc, copper and magnesium status in insulin-dependent diabetes. *Diabetes Res*, 26(1):41–45.

Kazi, T. G., Afridi, H. I., Kazi, N., Jamali, M. K., Arain,

M. B., Jalbani, N. 2008. chromium, manganese, iron, nickel, and zinc levels in biological samples of diabetes mellitus patients. *Biological Trace Ele- ment Research*, 1(1-18).

Kelly, F. 1998. Use of antioxidants in the prevention and treatment of disease. *Journal of the Interna- tional Federation of Clinical Chemistry.* , 10(1):21– 23.

Khan, A. R. 2014. Awan FR. Metals in the patho- genesis of type 2 diabetes. *Journal of Diabetes* *& Metabolic Disorders*, 2014(13).

Kratz, A., Ferraro, M. 2004. Sluss PM, Lewandrowski KB. Laboratory reference values. *New England Journal of Medicine*, 351:1548–64.

Kruse-Jarres, J., Rükgauer, M. 2000. Trace ele- ments in diabetes mellitus. Peculiarities and clini- cal validity of determinations in blood cells. *Jour- nal of trace elements in medicine and biology*, 1(21- 7).

Leonhardt, W., Hanefeld, M., Müller, G., Hora, C., Meissner, D., Lattke, P. 1996. Impact of concentra- tions of glycated hemoglobin, *α*-tocopherol, cop- per, and manganese on oxidation of low-density lipoproteins in patients with type I diabetes, type II diabetes and control subjects. *Clinica chimica acta*, 254(2):173–186.

Liu, Y., Liu, S., Mao, J., Piao, S., Qin, J., Peng, S. 2018.

Serum trace elements profile in graves’ disease patients with or without orbitopathy in Northeast. *China. BioMed research international*, 2018(2018).

Lowe, J., da Silva, R. T. 2017. Dissecting copper homeostasis in diabetes mellitus. *IUBMB L**ife*, 69(4):255–262. IUBMB life.

Montonen, J., Boeing, H., Steffen, A., Lehmann, R., Fritsche, A., Joost, H. G. 2012. Body iron stores and risk of type 2 diabetes: results from the Euro-

pean Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study. *Diabetologia*, 10(2613-21).

Moussa, S. 2008. Oxidative stress in diabetes melli- tus. *Romanian J*, 3(225-36).

Muslih, R. K. 2002. Al-Nimer MS, AL-ZAMELY O.

The level of malondialdehyde after activation with (H2O2) and (CuSO4) and inhibition by desferox- amine and molsidomine in the serum of patients with acute myocardial infarction. *National jour- nal of chemistry*, 5:139–48.

Noto, R., Alicata, R., Sfogliano, L., Neri, S., Bifarella,

M. 1984. A study of cupremia in a group of elderly diabetics. *Acta diabetologia*, 20(1):81–86.

Organization, W. H. 2009. *Global health risks: mor- tality and burden of disease attributable to selected major risks*. World Health Organization, Geneva.

Ozturk, P., Kurutas, E. B., Ataseven, A. 2013. Cop- per/zinc and copper/selenium ratios, and oxida- tive stress as biochemical markers in recurrent aphthous stomatitis. *Journal of Trace Elements in Medicine and Biology*, 4(312-6).

Pidduck, H. G. 1970. Wren PJ, Evans DAP. Plasma zinc and copper in diabetes mellitus. *Diabetes*, 4(234- 9).

Qiu, Q., Zhang, F., Zhu, W., Wu, J., Liang, M. 2017. Cop- per in diabetes mellitus: a meta-analysis and sys- tematic review of plasma and serum studies. Bio- logical trace element. *research*, 1(53-63).

Rohn, R. D., Pleban, P., Jenkins, L. 1993. Magne- sium, Zinc and copper in plasma and blood cellular components in children with IDDM. Clinica chim- ica acta. *Clin Chim Acta*, 15(1):21–8.

Rojas, D. R., Tegeder, I. 2018. Hypoxia-inducible fac- tor 1a protects peripheral sensory neurons from diabetic peripheral neuropathy by suppressing accumulation of reactive oxygen species. *J Mol Med (Berl)*, 96(12):1395–1405.

Saker, F., Ybarra, J., Leahy, P., Hanson, R. W. 1998. Kalhan SC, Ismail-Beigi F. Glycemia- lowering effect of cobalt chloride in the dia- betic rat: role of decreased gluconeogenesis. *American Journal of Physiology-Endocrinology and Metabolism*, 1998(274).

Salgueiro, M. J., Krebs, N. 2001. Zinc and dia- betes mellitus. *Biological Trace Element Research.*

, 81(3):215–228.

Sanjeevi, N., Freeland-Graves, J. 2018. Beretvas SN, Sachdev PK. Trace element status in type 2 dia- betes: a meta-analysis. Journal of clinical and diag- nostic research. *JCDR*, 2018(12).

Siddiqui, K., Bawazeer, N., Joy, S. S. 2014. Variation in

macro and trace elements in progression of type 2 diabetes. *The Scientific World Journal*, pages 1–9.

Simcox, J. A., McClain, D. A. 2013. Iron and diabetes risk. *Cell*, 3(329-41).

Sun, W., Yang, J., Wang, W., Hou, J., Cheng, Y., Fu, Y. 2018. The beneficial effects of Zn on Akt-mediated insulin and cell survival signaling pathways in dia- betes. *Journal of Trace Elements in Medicine and Biology*, 46:117–27.

Tang, X., Shay, N. 2001. Zinc has an insulin- like effect on glucose transport mediated by phosphoinositol-3-kinase and Akt in 3T3-L1 fibroblasts and adipocytes. *The Journal of nutrition*, 131(5):1414–1420.

Triggiani, V. 2006. Resta F, Guastamacchia E, Sabba C, Licchelli B, Ghiyasaldin S, et al. Role of antiox- idants, essential fatty acids, carnitine, vitamins, phytochemicals and trace elements in the treat- ment of diabetes mellitus and its chronic compli- cations. *Endocrine, Metabolic & Immune Disorders- Drug Targets (Formerly Current Drug Targets- Immune, Endocrine & Metabolic Disorders)*, 1(77- 93).

Tuvemo, T. 1983. Gebre-Medhin M. The role of trace elements in juvenile diabetes mellitus. *Pediatri- cian*, 4(213-9).

Viktorinova, A., Tošerová, E. 2009. Križko M, Ďuračková Z. Altered metabolism of copper, zinc, and magnesium is associated with increased levels of glycated hemoglobin in patients with diabetes mellitus. *Metabolism*, 10(1477-82).

Vincent, A. M., Russell, J. W., Low, P., Feldman, E. L. 2004. Oxidative stress in the pathogenesis of dia- betic neuropathy. *Endocrine reviews*, 4(612-28).

Walter, R. M., Uriu-Hare, J. Y., Olin, K. L., Oster, M. H., Anawalt, B. D., Critchfield, J. W. 1991. Copper, zinc, manganese, and magnesium status and com- plications of diabetes mellitus. *Diabetes Care*, 14(11):1050–1056.

Watts, D. L. 2003. race elements and glucose disor- ders. Townsend Letter for Doctors and Patients. . (245):68–72.

Wiernsperger, N., Rapin, J. 2010. Trace elements in glucometabolic disorders: an update. *Diabetology & metabolic*, 2010(2).

Wijesekara, N., Chimienti, F., Wheeler, M. 2009. Zinc, a regulator of islet function and glucose homeosta- sis. *Diabetes, Obesity and Metabolism*, 11:202–14.

Wolide, A. D., Zawdie, B., Alemayehu, T., Tadesse, S. 2017. Association of trace metal elements with lipid profiles in type 2 diabetes mellitus patients: a cross sectional study. *BMC endocrine*, 2017(17).

Yildirim, Ö., Büyükbingöl, Z. 2003. Effect of cobalt on the oxidative status in heart and aorta of streptozotocin-induced diabetic rats. Cell bio- chemistry and function. *Cell Biochem Funct*, 21(1):27–33.

Zheng, Y., Li, X. K., Wang, Y., Cai, L. 2008. The role of zinc, copper and iron in the pathogenesis of diabetes and diabetic complications: therapeutic effects by chelators. *Hemoglobin*, 32(1-2).

Zinc, T. C. 2005. the pancreas, and diabetes: insights from rodent studies and future directions. *Biomet- als*, 4(305-12).