Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i7.6907

EVALUATE AND ANALYZE OF TRACE ELEMENTS IN TYPE 2 DIABETES MELLITUS

Harjeet Singh[1], Dr Jaya Jain[2], Dr Ashutosh Jain[3], Dr Chaudhary Devendra[4*]

[1]Tutor, Dept. of Biochemistry, GMC, Ambedkar Nagar (UP)
[2]Professor Dept. of Biochemistry, Index Medical College Hospital and Research Centre , Indore, MP
[3]Assistant Professor Dept, of Physiology, Index Medical College Hospital and Research Centre , Indore, MP
[4*]Assistant Professor, Dept. of Microbiology, Rajshree Medical Research Institute & Hospital, Bareilly, UP

***Corresponding Author:**Dr Chaudhary Devendra
*Assistant Professor, Dept. of Microbiology, Rajshree Medical Research Institute & Hospital, Bareilly, UP, dchaudhary201@gmail.com

Abstract

Background: As Diabetes Mellitus is a metabolic disorder, where metabolism of various trace elements is being altered. Present study has been carried out to find out the association between Diabetes Mellitus and alteration in the level of trace elements.

Aim: To analyse the level of trace elements in type 2 DM patients in comparison with healthy controls.

Materials and Methods: The present cross sectional study was carried out in 122 patient of Type 2 Diabetes Mellitus. The study was carried out in Clinical biochemistry, central Laboratory, IMCH and RC, Department of Biochemistry, Indore. FBS was estimated by GOD-POD method. Serum Copper and Serum Zinc levels were assessed colorimetrically.

Results: In our study, serum copper level was found high in Type 2 DM patients and serum Zinc level is decrease ed in the patients of Type 2 DM.

Conclusion: Alteration in levels of Copper and Zinc are found to be important predisposing factors for patients of diabetes mellitus for developing complications. From the present study it may be concluded that alteration in levels of trace elements like Cu and Zn may have a role in the pathogenesis and progression of Diabetes Mellitus.

Keywords: Diabetes Mellitus, zinc, copper, selenium, Iron

Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia caused by insulin secretion, insulin action, or both. Diabetes-related chronic hyperglycemia has been linked to long-term organ damage, dysfunction, and failure, including the eyes, kidneys, nerves, heart, and blood vessels.[1] Diabetes is a widespread disease in developed countries and is the fourth leading cause of mortality. [2] According to the "International Diabetes Federation," Atlas 10th Edition (2021), a total of 537 million adults (20-79 years old) have diabetes mellitus. By 2030, this figure is expected to reach 643 million, and by 2045, it will reach 783 million. In addition, it is anticipated that 541

million individuals would have impaired glucose tolerance by 2021. In 2021, nearly 6.7 million persons aged 20–79 is expected to die from diabetes-related causes. [3]

Diabetes is rapidly approaching epidemic levels in India, with over 62 million diabetics presently diagnosed. In the year 2000, India (31.7 million people) had the highest number of people with diabetes mellitus worldwide, followed by China (20.8 million) and the United States (17.7 million). According to Wild et al, the global prevalence of diabetes is expected to double from 171 million people in 2000 to 366 million people in 2030, with India experiencing the greatest growth. Diabetes mellitus is expected to impact up to 79.4 million people in India by 2030, with considerable rises in the number of people afflicted in China (42.3 million) and the United States (30.3 million) as well.[4]

Significant changes in the metabolism of minerals, including trace elements (zinc, selenium, copper, iron, chromium, manganese & magnesium) and inflammatory markers (c reactive protein & interleukin 4) have been described in patients with diabetes mellitus, and several mineral deficiencies have been associated with some of the complications of diabetes. [5]

Selenium (Se) controls β-cell target genes, promotes development in pancreatic islet function and protection for tissues and membranes from oxidative strain. If Se levels exceed optimum values, it can cause a diabetogenic impact by defecting insulin responsiveness, growing rates of glycolysis, and promoting the release of glucagon. Hence, promoting hyperglycemia or inducing over expression of antioxidant selenoproteins may result in insulin resistance and obesity. zinc is present in secretory vesicles within β-cells of the pancreas where it participates in the crystallization/storage of insulin and is thus released alongside insulin into the plasma [9]. Deficiency of zinc disrupts insulin homeostasis, resulting in a reduction of insulin secretion by β-cells.[6] This may be due to the fact that magnesium ionsare an essential cofactor in several processes. increases the affinity of insulin receptors for ATP and is thus essential for their auto-phosphorylation and tyrosine kinase activity, which results in magnesium sensitising cells to insulin.

The role of copper in glucose homeostasis is not well defined. Experimental data suggest that impairment of glucose tolerance can be secondary to a Cu-deficiency.[7]
Manganese (Mn) is another essential trace element which has been previously observed to control blood sugar and cellular energy, immunity system functions, and processes of defense against free radicals. It works as a cofactor in different enzymes like those involved in mitochondrial glycoprotein synthesis.[8]

Free iron serves as a catalyst for lipid and protein oxidation and the formation of reactive oxygen species. In addition, iron indices are correlated with obesity and insulin sensitivity. In the presence of hyperglycemia and inflammation, iron may contribute to the development and progression of oxidative injury. Iron may also negatively impact on glucose control. [9]

In carbohydrate metabolism, Zinc has an important role. [10] Various studies have shown that biological activity of insulin is being increased in vitro by Zinc. Further decreased level of Zinc may increase the insulin resistance in NIDDM. [11] Derangement in the metabolism of copper can be a cause of chronic complications of diabetes mellitus. [12] It has been postulated that high level of Copper is associated with increased oxidative stress. Oxidative stress is linked with impairment in glucose tolerance and insulin resistance. [13] So estimation of Copper and Zinc is an important parameter for management of type 2 DM. The present study aimed to analyse the level of trace elements (Coppe, selenium, iron and Zinc) in type 2 DM patients in comparison with healthy controls.

Materials and Methods

The study was conducted in IMCH and RC, Department of Biochemistry. Ethical clearances was obtained from the Institutional Ethical Committee and written informed consent was taken, before carrying out the study.

Sample size

A total of 122 subjects was recruited, 61 severe diabetes mellitus patients of cases group in Department of Biochemistry, Index Medical College & Research Centre, and 61 healthy controls.

Sample Collection

Overnight fasting 5 ml of blood was drawn from the antecubital vein of all the study participants.

Statistics Analysis

Mean ± SD were calculated for all the parameters to examine and were differentiated by Student's t-test using SPSS 23. P-values considered significant were as follows: – $P < 0.05$– a Significant and $P > 0.001$ –a highly Significant.

Result

The study was conducted with 122 case and 122 control. The purpose to conduct the plot study is to find out the feasibility for conducting the study and design on plan of statistical analysis.

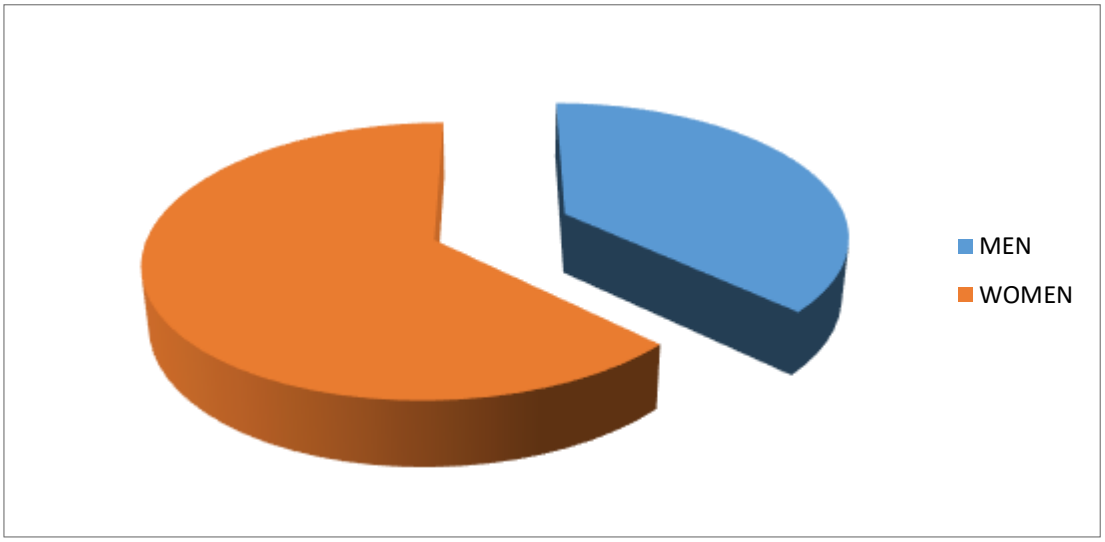

Figure no.1: Compare to male and female type 2 diabetes mellitus

Table no.1 : Comparative study of Trace elements in Control and Diabetes Mellitus Patients.

Parameter	Controls (Mean±SD) (n=122)	Diabetes Mellitus (Mean±SD) (n=100)	p-value
SERUM HbA1C%	5.51± 1.07	6.49± .59	0.0001
SERUM FBS (mg/dl)	84.09 ±8.76	122.09 ± 8.98	0.0001
SERUM ZINC (µg/dl)	77.46 ± 14.60	71.82 ± 15.79	0.0427
SERUM SELENIUM (µg/dl)	62.80 ±16.38	70.99 ±13.79	0.0034
SERUM COPPER (µg/dl)	55.92 ±20.89	63.62 ±18.28	0.0323
SERUM IRON (µg/dl)	99.72 ±38.09	140.2±48.86	0.0001

In the present study, HbA1C (6.49± .59), FBS (122.09 ± 8.98), S.zinc (122.09 ± 8.98), S. Selenium(71.82 ± 15.79) , S. Copper (63.62 ±18.28) and S Iron (140.2±48.86) levels were significantly increased in type 2 diabetes mellitus patients compared with controls. Serum zinc

(77.46 ± 14.60) levels were significantly decreased in type 2 diabetes mellitus patients compared with controls as illustrated in table 1

Discussion

Trace elements have been considered as essential for optimum health. [14] The clinical importance of trace elements is still controversial. Among the trace elements, copper and zinc are of particular importance. [15] In modern era, chronic disorders such as diabetes mellitus and hyper tension are major causes of death world wide. [16] Sufficient evidences are present which shows alteration in metabolism of several trace elements in diabetes mellitus. [17-18] Zinc is a dietary metal required for the healthy functioning of the body. Zinc is one of the most important trace elements in the body and it is essential as a catalytic, structural and regulatory ion. It is involved in homeostasis, in immune responses, in oxidative stress, in apoptosis and in ageing. Zinc deficiency is linked to decreased immunity leading to increased infection susceptibility. But the role of Zn in the prevention, treatment and complications of DM is not clear. [19]

In the present study, we significantly low in serum iron level in Type 2 diabetes mellitus patients. Our study showed a decrease in serum level of zinc (71.82±15.79) in cases as compared with the controls group which was (77.46±14.60). This finding shows the level of serum zinc was significant between cases as compared to controls.These results were consistent with a previous study done by Sahria and Goswami, [20] which also showed low levels of Zn in diabetic patients compared to their controls ($P < 0.05$). This finding also concurred with studies done by Saha-Roy et al. [21] and Masood et al.Al-Maroof and Al-Sharbatti [20, 22] also observed significantly lower serum Zn levels in diabetics than in control subjects. Marchesini et al [23] explained that low Zn seen in the diabetic population was due to the decreased gastrointestinal absorption and increased urinary excretion. In one study, the Zn levels were reported as similar in diabetic and control subjects [24] However, a study done by Mamza et al. revealed high Zn levels in diabetic patients [25]

In our study, we evaluated the status of serum selenium level in Type 2 diabetes mellitus patients. Our study showed an increase in serum level of Se (70.99±13.79) in cases as compared with the controls group which was (62.80±16.38). This finding shows the level of serum Se was significant between cases as compared to controls.Impaired Se homeostasis was frequently associated with either hyper- or hypoinsulinemia in the animal models discussed above. A likely explanation for these observations stems from the fragile redox homeostasis in pancreatic β-cells and the role of selenoenzymes therein [25-26]. Tiedge.M et. al explained that low activity of the common antioxidant enzymes, superoxide dismutase, catalase, and GPX [27]

Iron is one of the essential trace elements for the human body. The body contains 3–5 g iron. The body regulates the amount of iron mainly through absorption. When iron is deficient or excessive, it causes dysfunction of the body. Excessive iron stores have been suggested to be associated with a high risk of type 2 diabetes by causing damage to the pancreatic β-cells and insulin resistance through increased oxidative stress [28] In the present study, we evaluated the status of serum iron level in Type 2 diabetes mellitus patients. Our study showed a increase in serum level of iron (140.27±48.86) in cases as compared with the controls group which was (99.72±38.09). This finding shows the level of serum iron was significant between cases as compared to controls.

Most of the studies reported in our review show an association between advanced age and higher copper levels in patients with diabetes and our study, we evaluated the status of serum copper level in Type 2 diabetes mellitus patients. Our study showed a increase in serum level of copper (63.62±20.89) in cases as compared with the controls group which was (55.92±38.09). This finding shows the level of serum copper was significant between cases as compared to controls.

The increase in Cu ion levels in patients with diabetes mellitus may be attributed to hyperglycaemia that may stimulate glycation and release of copper ions and this accelerates the oxidative stress, so that, Advanced Glycation End products are formed, that are involved in the pathogenesis of diabetic

complications [29] Majority of plasma copper is transported bound to ceruloplasmin (>95%); rest is bound to albumin, transcuprein and copper-amino acid complexes. Ceruloplasmin is an acute phase reactant, has ferro-O2-oxidoreductase (pro-oxidant) activity directed towards ferrous ion stimulated lipid peroxidation and formation of hydroxyl radical in Fenton reaction. [30]
In our study Zn levels in diabetic patients was significantly lower ($p<0.0001$) compared to controls which matches with earlier studies. [31] Copper (Cu) is an essential trace element that is required for physiological function of number of enzymes. Copper has important role in synthesis of hemoglobin and immune function.
Increase in level of Copper, particularly the free fraction, may produce tissue injury apparently due to its pro-oxidant effects and the depletion of anti-oxidant reserves. [32] Major transported form of Copper is bind with ceruloplasmin (>95%); rest is bound to albumin, transcuprein and copperamino ac id complexes. Copper is harmful in its unbound form, c auses redox imbalance due to it's highly redox active nature, in which there is activation of stress sensitive intracel lular signalling pathways through Haber-Weiss reaction. [33]

The rise in Copper ion levels in diabetes mellitus patients may be due to hyperglycaemia that may enhance glycation and release of copper ions and this increases the oxidative stress, so that, Advanced Glycation end products are produce which are involved in the pathogenesis of diabetic complications. [34] Copper like transition metal has greater affinity to attach with glycated proteins. In our study there
is higher level of copper in patients of DM than the controls which correlates with other studies.[35]

Conclusion

Alteration in levels of Copper and Zinc are found to be important predisposing factors for patients of diabetes mellitus for developing complications. From the present study it may be concluded that alteration in levels of trace elements like Cu and Zn may have a role in the pathogenesis and progression of Diabetes Mellitus. The decreased blood levels of Zn and increased blood levels of Cu as have been found in present study can be utilized for prognosis and management of diabetes mellitus. As there is vital role of trace elements like zinc and copper in diabetes mellitus, it is advised that sufficient provision of these trace elements in the diet of diabetic patients can be helpful in the long term management of diabetic patients. For better understanding effect of these trace elements in diabetes mellitus, further clinical studies are needed which should enroll larger number of patients and uses higher advanced methods.

Reference

1. American Diabetes Association Professional Practice Committee; 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care 1 January 2022; 45 (Supplement_1): S17–S38.
2. Burtis, C. A., Bruns, D.E, (2016) Tietz Fundamental of Clinical Chemistry & Molecular Diagnostics: Diabetes (7th Edition). Elsevier
3. International Diabetes Federation, Atlas 2021 – 10th edition, www.diabetesatlas.org
4. Kaveeshwar, S. A., & Cornwall, J. (2014). The current state of diabetes mellitus in India. The Australasian medical journal, 7(1), 45–48.
5. Stanimirovic J, Radovanovic J, Banjac K, Obradovic M, Essack M, Zafirovic S, Gluvic Z, Gojobori T, Isenovic ER. Role of C-Reactive Protein in Diabetic Inflammation. Mediators Inflamm. 2022 May 17;2022:3706508.
6. Sobczak, A. I. S., Stefanowicz, F., Pitt, S. J., Ajjan, R. A., & Stewart, A. J. (2019). Total plasma magnesium, zinc, copper and selenium concentrations in type-I and type-II diabetes. BioMetals
7. Ruíz C, Alegría A, Barberá R, Farré R, Lagarda J. Selenium, zinc and copper in plasma of patients with type 1 diabetes mellitus in different metabolic control states. J Trace Elem Med Biol. 1998 Jul;12(2):91-5.

8. Yakout S, Faqeeh F, Al-Attas O, Hussain SD, Saadawy GM, Al-Daghri NM, Alokail MS. Patterns of essential trace elements (Cr, Mn, Ni, and Se) in Saudi patients with type 2 diabetes mellitus. Am J Transl Res. 2022 Nov 15;14(11):8175-8182.
9. Kazi, T. G., Afridi, H. I., Kazi, N., Jamali, M. K., Arain, M. B., Jalbani, N., &Kandhro, G. A. (2008). Copper, Chromium, Manganese, Iron, Nickel, and Zinc Levels in Biological Samples of Diabetes Mellitus Patients. Biological Trace Element Research, 122(1), 1–18.
10. Chausmer AB. Zinc, Insulin and Diabetes. J Am Coll Nutr. 1998;17(2):109–115.
11. Arquilla ER, Packer S, Tarmas W, Miyamoto S. The Effect of Zinc on Insulin Metabolism*. Endocrinol. 1978;103(4):1440–1449
12. Zheng Y, Li XK, Wang Y, Cai L. The role of zinc, copper and iron in the pathogenesis of diabetes and diabetic complications: therapeutic effects by chelators. Hemoglobin. 2008;32:135–145.
13. Park K, Gross M, Lee DH, Holvoet P, Himes JH, et al. Oxidative Stress and Insulin Resistance: The Coronary Artery Risk Development in Young Adults study. Diabetes Care. 2009;32(7):1302–1307.
14. Mooradian AD, Morley JE. Micronutrient status in diabetes mellitus. Am J Clin Nutr. 1987;45(5):877–895. doi:10.1093/ajcn/45.5.877.
15. Dormonday TL. Trace element analysis of hair. BMJ. 1986;293:975– 976.World health Organisation document. Diabetes. 2005.
16. Walter RM, Uriu-Hare JY, Olin KL, Oster MH, Anawalt BD, et al. Copper, Zinc, Manganese, and Magnesium Status and Complications of Diabetes Mellitus. Diabetes Care. 1991;14(11):1050–1056.
17. Fujimoto S. Studies on the relationship between blood trace metal concentration and the clinical status of patients with cerebrovascular disease, gastric cancer and diabetes mellitus. Hokoido Igaku Zasshi. 1987;62:913–932.
18. Salwen M. Vitamins and trace elements, McPherson: Henry's Clinical Diagnosis and Management by Laboratory Methods. vol. 22nd edn. ; 2011,. p. 417–428.
19. Chausmer AB. Zinc, Insulin and Diabetes. J Am Coll Nutr. 1998;17(2):109–115.
20. Saharia GK, Goswami RK. Evaluation of serum zinc status and glycated hemoglobin of type 2 diabetes mellitus patients in a tertiary care hospital of Assam. J Lab Physicians. 2013;5:30–3.
21. Saha-Roy S, Swati B, Choudhury Kanika M, Santasmita L, Aruna B, Gargi S, et al. Status of serum magnesium, zinc and copper in patients suffering from type-2 diabetes mellitus. J Drug Deliv Ther. 2014;4:70–2.
22. Masood N, Baloch GH, Ghori RA, Memon IA, Memon MA, Memon MS. Serum zinc and magnesium in type-2 diabetic patients. J Coll Physicians Surg Pak. 2009;19:483–6.
23. Marchesini G, Bugianesi E, Ronchi M, Flamia R, Thomaseth K, Pacini G. Zinc supplementation improves glucose disposal in patients with cirrhosis. Metabolism. 1998;47:792–8.
24. Zargar AH, Shah NA, Masoodi SR, Laway BA, Dar FA, Khan AR, et al. Copper, zinc, and magnesium levels in non-insulin dependent diabetes mellitus. Postgrad Med J. 1998;74:665–8.
25. Mamza YP, Abdullahi ZA, Gali RM, Mshelia DS, Genesis RY, Habu SA. Status of serum zinc and magnesium among type 2 diabetic subjects in Maiduguri. J Dent Med Sci. 2016;15:66–70. Benakova S., Holendova B., Plecita-Hlavata L. Redox homeostasis in pancreatic beta-cells: from development to failure. Antioxidants. 2021;10(4)
26. Steinbrenner H. Interference of selenium and selenoproteins with the insulin-regulated carbohydrate and lipid metabolism. Free Radic. Biol. Med. 2013;65:1538–1547.
27. Tiedge M., Lortz S., Drinkgern J., Lenzen S. Relation between antioxidant enzyme gene expression and antioxidative defense status of insulin-producing cells. Diabetes. 1997;46(11):1733–1742.
28. Liu J, Li Q, Yang Y, Ma L. Iron metabolism and type 2 diabetes mellitus: A meta-analysis and systematic review. J Diabetes Investig. 2020 Jul;11(4):946-955.

29. Abdul hamidzargar, Nissar ahmad shah, Shariq rashidmasoodi,et al. Copper, Zinc, and Magnesium levels in non-insulin dependent Diabetes mellitus 1998;74:665-668
30. Nataraj, N., Karthik, G., Shantha Kumari, N., & Srinivasa, K. V. (2021). Comparative study of copper, zinc levels in uncontrolled type 2 diabetes mellitus with normal subjects. International Journal of Health Sciences, 6(S4), 11748–11753.
31. Zheng Y, Li XK, Wang Y, Cai L. The role of zinc, copper and iron in the pathogenesis of diabetes and diabetic complications: therapeutic effects by chelators. Hemoglobin. 2008;32:135–145.
32. Maggini S, Wintergerst ES, Beveridge S, Hornig DH. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. British Journal of Nutrition. 2007;98(S1):S29–S35.
33. Cunninghamn J, Leffell M, Mearkle P, Harmatz P. Elevated plasma ceruloplasmin in insulin-dependent diabetes mellitus: Evidence for increased oxidative stress as a variable complication. Metabolism. 1995;44(8):996–999..
34. Abou-Seif MA, Youssef AA. Evaluation of some biochemical changes in diabetic patients. Clin Chim Acta. 2004;346(2):161–170.
35. Annan M, Raines DA. Urinary excretion of chromium, copper and manganese in diabetes mellitus and associated disorders. Diabetes Care. 1991;18:129–134.