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Investigation of Serum Zinc Level in Non-Diabetic, Pre-Diabetic And Diabetic Patients: A Prospective Cross-Sectional Study

Non-Diyabetik, Pre-Diyabetik ve Diyabetik Hastalarda Serum Çinko Düzeyinin İncelenmesi

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ABSTRACT

Aim: The aim of the study was to determine the serum zinc level in non-diabetic, pre-diabetic and diabetic patients and reveal the relationship between serum zinc level and glycemic status.

Material and Method: The study was a single-center, prospective, cross-sectional study. Fasting blood sugar, glycated hemoglobin, insulin resistance, and serum zinc levels of patients admitted to the internal medicine outpatient clinic were measured. Patients were categorized as non-diabetic, pre-diabetic, and diabetic according to their results, and compared regarding serum zinc levels.

Results: Zinc was significantly lower in the diabetes group than in the other groups (p<0.001), while there was no significant difference between non-diabetes and prediabetes groups. Zinc was negatively correlated with fasting blood sugar (r=-0.342, p<0.001), HOMA-IR (r=-0.344, p<0.001), and HbA1c (r=-0.327, p<0.001). Zinc had a sensitivity of 65.0%, specificity of 59.5%, accuracy of 61.3%, positive predictive value of 44.5%, and negative predictive value of 77.3% to predict diabetes for the cut-off point of 73 (AUC: 0.654, 95% CI: 0.588-0.720, p<0.001). In addition, multivariable logistic regression analysis revealed that low zinc (<73) was independently associated with the diabetes after adjusted by age and gender (OR: 2.618, 95% CI: 1.571-4.365, p<0.001).

Conclusion: While serum zinc levels were at similar levels in non-diabetic and pre-diabetic patients, they were significantly lower in diabetic patients, indicating that zinc levels decreased as glycemic control worsens. Measuring the serum zinc level in the risk group and replacing it if deficient may help prevent the development of diabetes by supporting glycemic control and reducing oxidative stress.

Key Words: Diabetes mellitus, İnsulin, Zinc, Trace elements

ÖZ

Amaç: Çalışmanın amacı non-diyabetik, pre-diyabetik ve diyabetik hastaların serum çinko düzeyini tespit ederek serum çinko düzeyi ile glisemik durum arasındaki ilişkiyi ortaya koymaktır.

Gereç ve Yöntem: Çalışma tek merkezli, prospektif ve kesitsel bir çalışmadır. İç hastalıkları polikliniğine başvuran hastaların açlık kan şekeri, glikolize hemoglobin, insülin rezistansı ve serum çinko düzeyleri ölçülmüştür. Hastalar sonuçlarına göre non-diyabetik, pre-diyabetik ve diyabetik olarak kategorize edilmiş ve serum çinko düzeyleri açısından karşılaştırılmışlardır.

Bulgular: Çinko diyabetik grupta non-diyabetik ve pre-diyabetik gruba göre anlamlı olarak düşüktü (p<0.001). Pre-diyabetik ve non-diyabetik grup arasında serum çinko düzeyleri açısından anlamlı farklılık yoktu. Çinko açlık kan şekeri (r=-0.342, p<0.001), insülin direnci (r=-0.344, p<0.001) ve glikolize hemoglobin (r=-0.327, p<0.001) ile negatif korelasyon göstermekteydi. Çinkonun 73 kesme değeri için diyabeti öngörmede %65,0 duyarlılığı, %59,5 özgüllüğü, %61,3 doğruluğu, %44,5 pozitif öngörü değeri ve %77,3 negatif öngörü değeri olduğu tespit edildi (AUC: 0.654, 95% CI: 0.588-0.720, p<0.001). Ek olarak, çok değişkenli lojistik regresyon analizi, düşük çinkonun (<73) yaş ve cinsiyetten bağımsız olarak diyabetle ilişkili olduğunu göstermiştir (OR: 2.618, 95% CI: 1.571-4.365, p<0.001).

Sonuç: Serum çinko düzeyinin non-diyabetik ve pre-diyabetik hastalarda benzer düzeylerdeyken diyabetik hastalarda anlamlı olarak düşük olması glisemik kontrol kötüleştikçe çinko seviyesinin düştüğünü göstermektedir. Riskli grupta serum çinko düzeyini ölçmek ve eksikse replase etmek glisemik kontrole destek olarak ve oksidatif stresi azaltarak diyabet gelişimini önlemeye yardımcı olabilir.

Anahtar Kelimeler: Diabetes mellitus, İnsülin, Çinko, Eser elementler

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Introduction

Type 2 diabetes is one of the most prevalent diseases in the world, and its prevalence increases every year (1). According to International Diabetes Federation data, in 2017, the number of diabetic patients between the ages of 20-99 was 451 million worldwide, and 90% of these cases were type 2 diabetic. This number is expected to increase to 690 million in 2045 (2). The prevalence of diabetes is higher, especially in low- and middle-income countries. Unhealthy eating habits play a significant role in the onset and progression of diabetes. Compelling evidence has established that a healthy diet can prevent diabetes to a considerable extent and can prevent the development of complications in existing diabetes. A healthy diet refers to a Mediterranean diet, and an essential part of it is that it is rich in trace elements (3).

Many studies in the literature have demonstrated the relationship between trace elements such as zinc, chromium, vanadium, manganese, molybdenum, and selenium with glucose metabolism. The common features of these trace elements are that they increase insulin sensitivity by activating insulin receptors, take part as cofactors in reactions in glucose metabolism and have antioxidant effects (4). In addition to all these functions, zinc has a different relationship with insulin. All synthesis, storage and secretion steps occur dependent on zinc. Moreover, zinc stands out with its preventive effect on beta cell destruction. For this reason, zinc is the trace element that has been the subject of most studies on diabetes. Zinc deficiency worsens blood sugar regulation through all these mechanisms. Although it has a vital role in glucose metabolism studies suggest that zinc homeostasis is altered, and serum zinc levels are low in diabetic patients (5). Therefore, there is a vicious circle between low zinc levels and diabetes.

The onset of diabetes occurs several years before the onset of the overt clinical picture. Diagnosis in the pre-diabetic period and initiation of treatment may prevent the emergence of an overt disease picture (6). Maintaining optimal zinc levels may be an optimal option for preventing the development of diabetes, improving the prognosis of existing diabetes, and potentially having favorable effects on complications. Although there are several studies in the literature comparing non-diabetic and diabetic patients in terms of serum zinc levels, there are very few studies assessing pre-diabetic patients.

The present study aimed to analyze non-diabetic, pre-diabetic, and diabetic patients in terms of serum zinc levels, and establish the relationship between glycemic control and serum zinc levels.

Material and Method

The study was a single-center, cross-sectional study. The approval for the study was obtained from Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Date: 25.05.2023, Number: E-10840098-772.02-3254, Decision No: 469), and the study was conducted in accordance with the Helsinki Declaration Principles. All patients were informed in detail about the purpose and procedure of the study, and their written informed consent was obtained. Non-diabetic, pre-diabetic, and diabetic male and female patients aged 30–60 years who were not using any medication for insulin resistance/diabetes and who applied to Istanbul Medipol University Hospital Internal Medicine outpatient clinic between June-October 2023 were included in the study, and convenience sampling was used.

Non-diabetes, pre-diabetes, and diabetes were classified based on fasting blood sugar (FBS), insulin resistance calculated using Homeostasis Model Assessment index (HOMA-IR), and glycated hemoglobin (HbA1c) levels using the American Diabetes Association Criteria (7). Based on these criteria, patients with FBS 70-100, HOMA-IR <2.4, and Hba1c <5.7 were included in the non-diabetic patient group; patients with FBS 100-126, HOMA-IR >2.4, and Hba1c 5.7-6.4 were included in the pre-diabetic patient group; and patients with FBS ≥126, HOMA-IR ≥2.4, and Hba1c ≥ 6.5 were included in the diabetic patient group. Patients <30 years of age and >60 years of age, body mass index (BMI) >30 kg/m2, patients with any diagnosed chronic disease, patients with a previous diagnosis of diabetes and/or using oral antidiabetic agents/insulin due to diabetes, patients with hypertension/arrhythmia detected during the examination, liver dysfunction, renal dysfunction, patients with thyroid dysfunction, anemia, active infection, smokers (patients who smoked one pack of cigarettes a day were considered current smokers), patients who were using any herbal agent/supplement, patients who had used a supplement containing zinc in the last six months, pregnant and breastfeeding women were excluded. The medication use status of the patients was both inquired about in the anamnesis and confirmed in the personal health record system of the Ministry of Health. Detailed physical examinations were performed after anamnesis. The height was measured using a stadiometer with an accuracy of 0.1 cm, and the body height was measured using a Tanita scale with an accuracy of 0.1 kg (Tanita Body Composition Analyzer, MC-780MA-N, Japan). The BMI was calculated as the body weight in kilograms divided by the square of the height in meters (kg/m2). Blood pressure was measured with an electronic device (Omron M3 Upper Arm Blood Pressure Monitor). Electrocardiograms were obtained (EDAN SE1200 12-channel ECG device). After 12 hours of fasting, venous blood samples were collected. FBS, HOMA-IR, Hba1c, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine, thyroid stimulating hormone (TSH), C-reactive protein (CRP), complete blood count, and serum zinc levels were all measured in the laboratory. Serum zinc concentration was measured using the Randox colorimetric assay for zinc (United Kingdom). For the measurement of serum zinc concentration, a 6 mL blood sample was taken into the heavy metal-free trace element tubes containing heparin. The blood was centrifuged at 2500 rpm for 10 minutes. Zinc concentrations were expressed in µg/dL. Patients were divided into three groups: non-diabetic, pre-diabetic, and diabetic. They were compared in terms of serum zinc levels.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Kolmogorov-Smirnov test was used to examine the conformity of the variables to normal distribution. Descriptive statistics were presented by using median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. Between groups analysis were performed by using Kruskal Wallis test for continuous variables due to non-normality of distribution and chi-square test for categorical variables. Pairwise comparisons were adjusted by using Bonferroni correction. Relationships between zinc and diabetes markers were evaluated by using Spearman correlation coefficients. Diabetes prediction performance of the zinc was evaluated by using Receiver Operating Characteristic (ROC) curve analysis. Unadjusted and adjusted (by age and gender) odds ratios were calculated by using logistic regression analysis. Two-tailed p-values of less than 0.05 were considered statistically significant.

Results

A total of 149 females and 151 males were included in the

study. Median age was 45 years (interquartile range 37 - 52, range 30 - 60). Each group (non-diabetes, prediabetes and diabetes) consisted of 100 individuals. Age was significantly higher in the diabetes group than in the other groups (p<0.001), while there was no significant difference between non-diabetes and prediabetes groups. We determined no significant differences between groups in terms of gender (p=0.991). FBS (p<0.001), HOMA-IR (p<0.001) and HbA1c (p<0.001) were significantly higher in the diabetes group than in the other groups and were significantly higher in the prediabetes group than in the non-diabetes group. Zinc was significantly lower in the diabetes group than in the other groups (p<0.001), while there was no significant difference between non-diabetes and prediabetes groups (Table 1) (Figure 1).

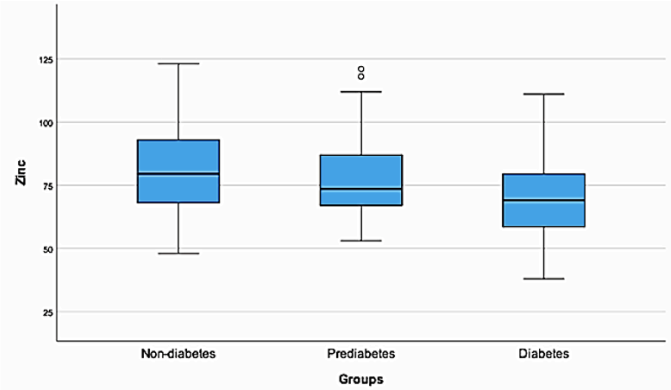

Figure 1. Box-plots of the zinc with regard to groups.

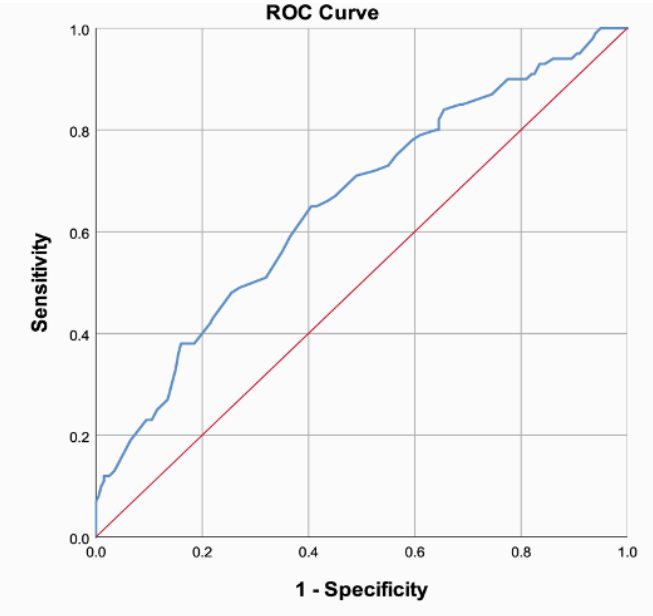

Figure 2. ROC curve of the zinc to predict diabetes.

Zinc was negatively correlated with fasting blood sugar (r=-0.342, p<0.001), HOMA-IR (r=-0.344, p<0.001) and HbA1c (r=-0.327, p<0.001) (Table 2). Zinc had a sensitivity of, specificity of 59.5%, accuracy of 61.3%, positive predictive value of 44.5%, and negative predictive value of 77.3% to predict diabetes for the cut-off point of 73 (AUC: 0.654, 95% CI: 0.588 - 0.720, p<0.001) (Figure 2). In addition, multivariable logistic regression analysis had revealed that low zinc (<73) was independently associated with the diabetes after adjusted by age and gender (OR: 2.618, 95% CI: 1.571 - 4.365, p<0.001) (Table 3).

Table 1. Summary of age, gender and laboratory measurements.

Variables	Non-diabetes (n=100)	Prediabetes (n=100)	Diabetes (n=100)	p value
Age	41.5 (34 - 48.5)	44 (37 - 51.5)	48 (43 - 54)*#	<0.001
Gender				
Female	48 (48.0%)	50 (50.0%)	51 (51.0%)	0.911
Male	52 (52.0%)	50 (50.0%)	49 (49.0%)	
FBS	81.5 mg/dL (76 - 90)	109 mg/dL (103 - 115.5)*	146 mg/dL (135.5 - 170)*#	<0.001
HOMA-IR	1.9 (1.5 - 2.0)	4.2 (3.1 - 7.05)*	9.2 (7.45 - 11.2)*#	<0.001
HbA1c	5.1 % (4.9 - 5.6)	6.0 % (6 - 6.2)*	7.45 % (6.9 - 8.8)*#	<0.001
Zinc	79.5 ug/dL (68 - 93)	73.5 ug/dL (67 - 87)	69 ug/dL (58.5 - 79.5)*#	<0.001

Descriptive statistics were presented by using median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.

*: Significantly different from "Non-diabetes", #: Significantly different from "Prediabetes"

Table 2. Correlations between zinc and diabetes markers.

	r	p value
FBS	-0.342	<0.001
HOMA-IR	-0.344	<0.001
HbA1c	-0.327	<0.001

r: Spearman correlation coefficient

Table 3. Performance of zinc to predict diabetes.

Cut-off	< 73
Sensitivity	65.0%
Specificity	59.5%
Accuracy	61.3%
PPV	44.5%
NPV	77.3%
AUC (95% CI)	0.654 (0.588 - 0.720)
p for AUC	<0.001
Unadjusted OR (95% CI)	2.728 (1.657 - 4.492)
p for unadjusted OR	<0.001
Adjusted OR (95% CI) (1)	2.618 (1.571 - 4.365)
p for adjusted OR	<0.001

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence interval, OR: Odds ratio, (1) Adjusted by age and gender.

Discussion

The present study revealed that serum zinc levels were significantly lower in diabetic patients than in both non-diabetic and pre-diabetic patients, but there was no significant difference between non-diabetic and pre-diabetic patients. Serum zinc level was negatively correlated with all parameters indicating poor glycemic course (high FBS, HOMA-IR, and HbA1c levels) assessed in our study. Furthermore, regression analyses indicated that low zinc levels (cut-off <73) were associated with diabetes independently of age and gender. Another result of

the study was that there was no significant difference between non-diabetic and pre-diabetic patients in terms of age. We included patients aged 30–60 years and found that the mean age of non-diabetic patients was 41.5 years, and the mean age of pre-diabetic patients was 44 years. Currently, the age of insulin resistance and pre-diabetes has decreased to a much younger age due to a high-calorie diet, a sedentary lifestyle, and increased stress. Although the mean age of diabetic patients in our study was significantly higher than the other two groups (mean age 48 years), this indicates that the pre-diabetic period rapidly progresses to diabetes without intervention, and the age of overt diabetes is early in Turkey.

The main factor in the development of type 2 diabetes is the development of resistance in muscle, fat, and liver cells to the hormone insulin, which allows circulating sugar to enter the cell and be used for energy production. Although high-calorie nutrition and sedentary life are the main mechanisms in the emergence of Type 2 diabetes, if we take a closer look at the pathophysiological mechanisms, it is possible to see how important trace element deficiencies play in the process. Understanding this relationship is especially important in bringing to mind options that may be beneficial in treatment.

Zinc is the second most abundant trace element in the human body after iron. Its total amount is about 2-3 grams, and its highest concentration is in pancreatic beta cells (8). Recognition of the relationship between insulin and zinc dates back almost to the discovery of insulin by Banting and Best in the 1920s. Zinc was first used in the 1930s to increase the half-life of insulin, which was started to be used in the form of injection for therapeutic purposes, and to make it more effective (9). In the 1970s, the biochemical structure of insulin and its pathways from secretion to synthesis were discovered. Insulin secreted as a monomer from pancreatic beta cells turns into a dimer in the presence of zinc and then three insulin dimers combine to form a hexamer (8). This is the stable form of insulin that is stored for secretion when needed. In 1994, Zalewski revealed that high sugar concentrations and other secretagogues that cause insulin secretion from the pancreas reduce islet cell zinc levels and that this is because zinc is used in all steps of synthesis, storage, and secretion of insulin (10). There is increased insulin release from pancreatic beta cells due to insulin resistance in the prediabetes stage. Since insulin and zinc are secreted together, this causes intracellular zinc loss. If the lost zinc is not replaced, over time the cell's insulin response to high sugar concentrations decreases and fasting blood sugar starts to rise. This is the transition period from prediabetes to diabetes, and zinc depletion also plays a role in this transition. Both animal and human studies have demonstrated that glucose-stimulated insulin secretion is significantly reduced in zinc deficiency (11). Another effect of zinc on insulin pathways is that it activates insulin-sensitive receptors in liver, fat and muscle cells and increases the insulin sensitivity of the cells and thus the insulin effect (12).

Zinc's association with diabetes is not limited to its effect on insulin pathways. Diabetes is a disease in which oxidative stress is significantly increased. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) are the three major enzymes that protect the cell against oxidative stress and free radicals, and all of these enzymes are zinc-dependent (13). In other words, we can say that zinc protects our cells against oxidative stress, especially pancreatic beta cells, where it is most abundant.

Zinc has a crucial role in blood sugar regulation, but diabetic patients are more prone to zinc loss. Urinary zinc excretion is increased in diabetic patients. This leads to a decrease in total body zinc (14). The reason for the increase in urinary zinc excretion in diabetic patients is osmotic diuresis and polyuria caused by glucosuria. Therefore, it is expected that the higher the blood sugar level, the higher the zinc loss. This is compensated by increased zinc absorption from the gastrointestinal system in the prediabetes stage (15). This mechanism may be one of the reasons why we found similar serum zinc levels in non-diabetic and pre-diabetic patients in our study. However, as diabetes progresses, zinc reabsorption pathways from the gastrointestinal tract are also adversely affected. Zinc leaks into the intestinal lumen due to increased inflammation in the intestines in diabetic patients and is excreted more with stool (16). Thus, we can conclude that zinc concentration is decreased in diabetic patients due to both the urinary and gastrointestinal systems being affected.

Consistent with our results, in studies designed similar to our study, serum zinc levels of type 2 diabetic patients were found to be lower than non-diabetics, and low zinc levels were associated with poor glycemic control. (17,18). Unlike the studies in the literature, we assessed not only the non-diabetic control group and the overt diabetes group but also the pre-diabetic group (FBS 100-126 / HOMA-IR > 2.4). Furthermore, all of the patients included in our study were newly diagnosed diabetic patients or patients who were diagnosed with diabetes but did not use any oral antidiabetic agent / insulin, so zinc levels were not affected by the use of any anti-diabetic agent.

There are numerous studies on diabetes complications and zinc in the literature. In a study on how serum zinc level affects microvascular complications in type 2 diabetic patients, patients with less than two microvascular complications and patients with at least two microvascular complications were compared. Patients with at least two microvascular complications had significantly lower serum zinc levels (19).

After revealing the positive effects of zinc replacement on blood sugar regulation in diabetic animals and humans, the effect of replacement on diabetic complications was examined. Cardiovascular diseases are the most common cause of death in type 2 diabetes. A meta-analysis examining 14 studies found that diabetic patients with high serum zinc levels had a significantly lower risk of cardiovascular disease than patients with low serum zinc levels (20).

Various animal and human studies have shown that zinc replacement has positive effects on diabetic nephropathy, neuropathy and retinopathy (21-23). It is possible to say that zinc replacement in diabetic patients both improves glycemic control and protects against various complications.

Although the beneficial effects of zinc on glycemic control and complications have been demonstrated in diabetic patients, zinc levels in non-diabetic patients have been found to have no effect on the development of diabetes. Zinc levels in the toenails of 3960 non-diabetic American young adults aged 20–32 years were measured in 1987. These patients were analyzed for the development of diabetes until 2010. A total of 418 cases of diabetes occurred. Patients in the highest and lowest quartile of zinc levels in the toenail were compared in terms of diabetes development, and no significant difference was found between them (24). A systematic review published in 2012 summarizing data from 3 studies on type 1 diabetes and 22 studies on type 2 diabetes indicated that zinc supplementation had positive effects on glycemic control in diabetic patients, but no effect of zinc supplementation on the risk of diabetes development in non-diabetic patients (25,26). The NHS cohort is one of the first study to explore the association between zinc intake and the risk of developing diabetes. This study revealed an increased risk of developing diabetes in participants with inadequate dietary zinc intake, but not a lower risk of diabetes in those with high dietary zinc intake (27). All these data show that zinc supplementation

may be beneficial in patients at high risk for diabetes and in diabetic patients, but that replacement must be performed after controlling zinc levels, and that replacement will be beneficial only in cases of deficiency; otherwise, no additional benefit can be obtained.

Conclusion

We observed that serum zinc concentrations were similar in non-diabetic and pre-diabetic patients but were significantly lower in diabetic patients compared to both groups. This is attributed to the fact that zinc homeostasis is maintained for a long time. However, as diabetes progresses, oxidative stress increases, renal zinc excretion increases due to hyperglycemia, and zinc absorption in the gastrointestinal tract decreases. Zinc may be a promising option since it prevents beta cell damage by enabling antioxidant enzymes to work effectively, functions in insulin synthesis, storage, and secretion, increases the insulin sensitivity of cells, prevents the development of diabetes in the high-risk group, improves the prognosis of existing diabetes, and has potentially positive effects on complications. However, it should be kept in mind that zinc replacement must be administered to the target patient group at the appropriate dose and duration after serum concentrations are checked.

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REFERENCES

1. Lovic D, Piperidou A, Zografou I, Grassos H, Pittaras A, Manolis A. The growing epidemic of diabetes mellitus. Curr Vasc Pharmacol. 2020;18(2):104-109.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes research and clinical practice. 2010;87(1):4-14.
3. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. The Lancet. 2014;383(9933):1999-2007.
4. Dubey P, Thakur V, Chattopadhyay M. Role of minerals and trace elements in diabetes and insulin resistance. Nutrients. 2020 Jun 23;12(6):1864.
5. Jansen J, Karges W, Rink L. Zinc and diabetes-Clinical links and molecular mechanisms. J Nutr Biochem 2009; 20:399-417.
6. Beagley J, Guariguata L, Weil C, Motala AA. Global estimates of undiagnosed diabetes in adults. Diabetes Res Clin Pract. 2014;103 150–160.
7. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and diagnosis of diabetes: Standards of care in diabetes-2023. Diabetes Care. 2023;46(Suppl 1):19-40.
8. Ikle JM, Gloyn AL. 100 years of insulin: A brief history of diabetes genetics: insights for pancreatic beta-cell development and function. J Endocrinol. 2021;250(3):23-35.
9. Attie AD, Tang QQ, Bornfeldt KE. The insulin centennial-100 years of milestones in biochemistry. J Biol Chem. 2021;297(5):101278.
10. Zalewski PD, Millard SH, Forbes IJ, et al. Video image analysis of labile zinc in viable pancreatic islet cells using a specific fluorescent probe for zinc. J Histochem Cytochem. 1994 Jul;42(7):877-84.
11. Li YV. Zinc and insulin in pancreatic beta-cells. Endocrine. 2014; 45:178-89.
12. Kelleher SL, McCormick NH, Velasquez V, Lopez V. Zinc in specialized secretory tissues: roles in thepancreas, prostate, andmammarygland. Adv Nutr. 2011;2(2):101-11.
13. Kloubert V, Rink L. Zinc as a micronutrient and its preventive role of oxidative damage in cells. Food Funct. 2015;6(10):3195-204.
14. Menke A, Guallar E, Cowie CC. Metals in urine and diabetes in US adults. Diabetes. 2016;65(1):164-71.
15. da Silva Bandeira V, Pires LV, Hashimoto LL, et al. Association of reduced zinc status with poor glycemic control in individuals with type 2 diabetes mellitus. J Trace Elem Med Biol. 2017;1(44):132-6.
16. Rungby J. Zinc, zinc transporters and diabetes. Diabetologia. 2010;53(8):1549-51.
17. Kumar DA, Priya VS, Jaiprabhu J, Ramalingam K. Serum copper and zinc levels significance in type 2 diabetic patients. Jour of Med Sc Tech; 2014;3(2):79-81.
18. Gagandeep DS, Shailaza S, Rahul R. Evaluation of trace elements and glycated hemoglobin in type 2 diabetes mellitus. World J Pharm Pharm Sci. 2015;4(5):940-7.
19. Puri M, Gujral U, Nayyar SB. Comparative study of serum zinc, magnesium and copper levels among patients of type 2 diabetes mellitus with and without microangiopathic complications. Innovative Journal of Medical and Health Science. 2013;3(6):274-8.
20. Chu A, Foster M, Samman S. Zincstatusand risk of cardiovascular diseases and type 2 diabetes mellitus-A systematic review of prospective cohort studies. Nutrients. 2016;8(11):707.
21. Liu F, Ma F, Kong G, Wu K, Deng Z, Wang H. Zinc supplementation alleviates diabetic peripheral neuropathy by inhibiting oxidative stress and upregulating metallothionein in peripheral nerves of diabetic rats. Biol Trace Elem Res. 2014;158:211-8.
22. Parham M, Amini M, Aminorroaya A, Heidarian E. Effect of zinc supplementation on microalbuminuria in patients with type 2 diabetes: A double blind, randomized, placebo-controlled, cross-over trial. Rev Diabet Stud. 2008;5(2):102-9.
23. Barman S, Srinivasan K. Zinc supplementation ameliorates diabetic cataract through modulation of crystallin proteins and polyol pathway in experimental rats. Biol Trace Elem Res. 2019;187:212-23.
24. Park JS, Xun P, Li J, et al. Longitudinal association between toenail zinc levels and the incidence of diabetes among American young adults: The CARDIA Trace Element Study. Sci Rep. 2016;6(1):23155.
25. Jayawardena R, Ranasinghe P, Galappatthy P, Malkanthi RL, Constantine GR, Katulanda P. Effects of zinc supplementation on diabetes mellitus: A systematic review and meta-analysis. Diabetol Metab Syndr. 2012;4(1):1-2.
26. Czernichow S, Couthouis A, Bertrais S, et al. Antioxidant supplementation does not affect fasting plasma glucose in the Supplementation with Antioxidant Vitamins and Minerals (SU. VI. MAX) study in France: Association with dietary intake and plasma concentrations. Am J Clin Nutr. 2006;84(2):395-9.
27. Sun Q, van Dam RM, Willett WC, Hu FB. Prospective study of zinc intake and risk of type 2 diabetes in women. Diabetes Care. 2009;32: 629-634.