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Original Article

Patterns of essential trace elements (Cr, Mn, Ni, and Se) in Saudi patients with type 2 diabetes mellitus

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Abstract: Objectives: Type 2 diabetes mellitus (T2DM) outcomes were observed to be influenced by circulating trace elements' status. The differences and correlations between serum levels of chromium (Cr), manganese (Mn), nickel (Ni), and selenium (Se) in Saudi patients with and without T2DM as well as those with prediabetes (pre-DM) were examined in this retrospective cross-sectional study. Methods: Anthropometrics and fasting blood samples were collected from 119 patients with T2DM (aged 41-64 years), 95 non-T2DM (aged 27-55 years), and 80 with pre-DM (aged 35-57 years). An inductively coupled plasma-mass spectrometer was used to measure trace minerals in the blood. Results: T2DM patients had significantly lower Mn serum concentrations than controls. There was no difference in Cr and Ni levels between groups. Serum Mn and Ni levels were lower in pre-DM subjects than controls. Serum Se concentrations were higher in pre-DM and T2DM patients than controls. In T2DM patients, serum Cr and Mn levels were inversely correlated with glucose, while Ni and Se levels were positively correlated with glucose in the T2DM group. Conclusions: Because of their roles in glucose metabolism, impaired trace element status may also play a role in T2DM pathogenesis. Appropriate dietary control and mineral supplementation are recommended.

Keywords: Type 2 diabetes, trace elements, Saudi

Introduction

Diabetes mellitus (DM) has become a major global public health problem in both developed and developing countries, with an overall prevalence of 10.5% among people aged 20 to 79 years as of 2021 [1]. In Saudi Arabia, the age-adjusted prevalence of diabetes was 31.6% in Riyadh alone in 2011 [2]. Type 2 diabetes (T2DM), which accounts for approximately 90% of all DM cases, is caused by ineffective insulin function and is the result of a complex interplay of genetic, epigenetic, and environmental factors [1].

On the other hand, glycated hemoglobin (HbA1c) is an essential indicator of glycemic control over time, as it reflects the average amount of blood glucose within the past three months. As the average concentration of circulating glucose rises, the fraction of HbA1c rises in parallel [3]. These alterations in HbA1c have been recently observed to be associated with several micronutrients, including trace elements [4].

Variations in circulating trace element levels could play an important role in glucose metabolism [5, 6]. For instance, chromium (Cr) is fundamental for the standard metabolism of carbohydrates and it has a crucial role in insulin function by enhancing cell glucose ingestion [6-8]. Also, Cr has been shown to modulate insulin response in multiple ways, including increased insulin receptor kinase activation and binding of insulin to cells [9-12].

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 [13]. Mn insufficiency may result in poor glucose metabolism [14]. It works as a cofactor in different enzymes like

those involved in mitochondrial glycoprotein synthesis [15]. Mn deficiency decreases activity of these enzymes, altering cartilage production [15]. Furthermore, Mn is a pyruvate carboxylase cofactor that has a role in the transformation of different non-sugar compounds into glucose by gluconeogenesis [16]. Also, exposure to Ni causes the release of free radicals in a variety of tissues [14]. Ni leads to a significant rise in induction of nitric oxide synthase (iNOS) from the pancreas in rats, resulting in hyperglycemia [17]. Another study in animal models showed that Ni can lead to hyperglycemia by increased hepatic glycogenolysis, increased pancreatic release of glucagon, gluconeogenesis or decreased peripheral consumption of glucose [17]. There are several studies that link circulating Ni with increased risk of T2DM [14, 18].

Selenium (Se) is an important component of many selenoproteins which function as essential enzymes for redox homeostasis and protect against oxidative stress and inflammation [19]. 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 [20].

In previous research, we investigated the relationships of trace elements (Cu, Fe, and Zn) in Saudi adult people with varying degrees of glycemia [21]. In order to expand this investigation, the goal of this study was to figure out the patterns of another group of essential trace elements (Cr, Mn, Ni, and Se) and their effect in the same subjects that have T2DM and pre-DM.

Materials and methods

A total of 294 adult Saudi participants aged 25-65 years (T2DM = 119, Pre-DM = 80, non-T2DM controls = 95) were included in this study. These patients' information was randomly extracted from a bigger database maintained by the Chair for Biomarkers of Chronic Diseases (CBCD) at King Saud University, KSU, Riyadh, Saudi Arabia. In brief, this database contains clinical information of Saudi adults aged 18 and above who participated in several diabetes prevention programs launched in different primary healthcare centers (PHCCs) [22-24]. The classification system followed was from the World Health Organization (WHO, 2004) [25]. People with fasting blood glucose levels of 7.1 mmol/l or higher were diagnosed with T2DM, whereas those with levels between 6.1 and 7.0 mmol/l were classified as pre-diabetic [22]. This study was approved by the King Saud University Ethics Committee (permission No. 8/25/454239) at the College of Science Research Center in Riyadh, Saudi Arabia. A general questionnaire, including demographics and medical history were completed by all participants. A physical examination was performed by the attending physician to ensure that no patients were suffering from life-threatening diseases such as heart, kidney, or liver disease or mental health issues. Body mass index (BMI, kg/m^2), waist-hip ratio (WHR), and systolic and diastolic blood pressure (mmHg) were measured by trained nurses, as in previous studies.

Trace element determination

A volume of 150 µL of nitric acid was added to Eppendorf tubes containing 150 µL of samples and 100 µL of hydrogen peroxide then centrifuged at 4400 rpm, for 10 min, at 4°C. The tubes then were placed a block digester and digested at 95°C, for 90 min. The tube volume was completed to 1 mL with distilled water and stored at 4°C. Before analysis 250 µL from each sample were completed to 3 mL with deionized water. The analytical determination of trace metals was administered by ICP-MS (Inductively Coupled Plasma-Mass Spectrometer): NexION 300 D (Perkin Elmer, USA).

Statistical analysis

SPSS version 21.0 was used to analyze the data. For normal variables, mean and standard deviations were used, and for non-normal variables, median (1st quartile-3rd quartile) was used. In addition, categorical data was given as percentages and frequencies (percentages). For normal variables, ANOVA was used to evaluate the significant mean difference between groups, whereas for non-normal variables, Kruskal Wallis was used to test the significant

Table 1. Characteristics of T2DM patients

Parameters	Control	Pre-DM	T2DM	*P*-value	*P*-value*
N	95	80	119	--	--
Age (years)	40.9±13.7	46.7±10.9	52.2±11.2[A,B]	0.000	--
Female/Male	68/27	49/31	57/62	0.002	--
BMI (kg/m^2)	29.9±6.0	32.6±7.6	31.8±6.0	0.017	--
WHR	0.9±0.1	0.9±0.1	1.0±0.1	0.003	0.13
Systolic blood pressure (mmHg)	112.3±10.3	124.3±14.1[A]	128.5±15.1[A]	<0.001	<0.001
Diastolic blood pressure (mmHg)	74.1±7.0	78.5±8.0	79.6±9.0	0.004	0.06

Note: Group with superscript A indicates that there is significant difference between this group and controls whereas group with superscript B indicates that there is significant difference between this group and pre-DM group. Data presented as Mean ± SD for normal variables while Median (1st Quartile-3rd Quartile) is presented for non-normal variables; *P*-values are obtained from one-way analysis of variance (ANOVA); all non-normal variables were log-transformed prior to parametric testing; *indicates *p*-value adjusted age, BMI and sex; P<0.05 considered significant. Type 2 Diabetes Mellitus (T2DM), Body Mass Index(BMI), Waist-Hip Ratio (WHR).

Table 2. Serum Cr, Mn, Ni, and Se levels of T2DM as compared with controls and pre-DM patients

Parameters	Control	Pre-DM	T2DM	*P*-value	*P*-value*
Cr (µg/l)	1.6±0.4	1.8±0.4[A]	1.5±0.4[B]	<0.001	<0.001
Mn (µg/l)	28.1 (24.2-33.5)	14.8 (11.7-20.4)[A]	6.6 (5.8-11.3)[A,B]	<0.001	<0.001
Ni (µg/l)	4.4 (3.5-5.9)	3.5 (2.2-4.0)	4.4 (3.6-5.3)[B]	<0.001	<0.001
Se (µg/l)	55.7 (37.7-70.9)	60.1 (36.5-88.4)	78.4 (44.9-115.4)[A,B]	0.001	0.32

Data presented as Mean ± SD for normal variables while Median (1st Quartile-3rd Quartile) is presented for non-normal variables; *P*-values are obtained from One-way analysis of variance (ANOVA); all non-normal variables were log-transformed prior to parametric testing; *indicates *p*-value adjusted Age, BMI and sex; P<0.05 considered significant. Note: Group with superscript A indicates that there is significant difference between this group and controls whereas group with superscript B indicates that there is significant difference between this and the pre-DM group. Type 2 Diabetes Mellitus (T2DM), Chromium (Cr), Manganese (Mn), Nickel (Ni), and Selenium (Se).

median difference between groups. To evaluate variations in proportions between categorical variables, the Chi-square test was performed. The Pearson correlation coefficient was employed to find a link between two variables. Prior to parametric testing, all non-normal variables were log-transformed. A P<0.05 was considered significant.

Results

The baseline characteristics of the subjects studied are shown in **Table 1**. A total of 40% of the 294 subjects had T2DM, 35% were in the control group, and the remaining 25% had pre-DM. The mean systolic and diastolic blood pressures were significantly higher in T2DM patients, as well as in the pre-DM group, when compared to healthy controls. The average age of a person with pre-DM is typically similar to an adult with diabetes (46.7 years and 52.2 years for T2DM). Pre-DM was less common (28%) in people over the age of 50, but it accounted for 82% of the total T2DM population. In terms of BMI, the majority of pre-DM and T2DM patients were overweight (BMI 25.00-29.99), with only a few subjects being obese (BMI 30).

Mean serum Cr levels in the pre-DM group were considerably greater than those in the control and T2DM patient groups, as shown in **Table 2**. The pre-DM group also had considerably lower mean serum Ni levels than the control group or the T2DM patients. T2DM patients also had significantly decreased mean serum Mn levels compared to pre-DM patients and controls. Finally, the mean serum Se levels of T2DM patients were higher than those of pre-DM patients and controls. Serum levels for each demographic are listed in **Table 2**. Differences in Cr, Mn, and Ni concentration were found between pre-DM and T2DM patients and controls after statistical analysis. The pre-DM patients had decreased Mn (14.8 g/l) and Ni (3.5 g/l) serum concentrations compared to the control group. Serum values of Cr (1.5 g/l) and Mn (6.6 g/l) were lower in T2DM patients

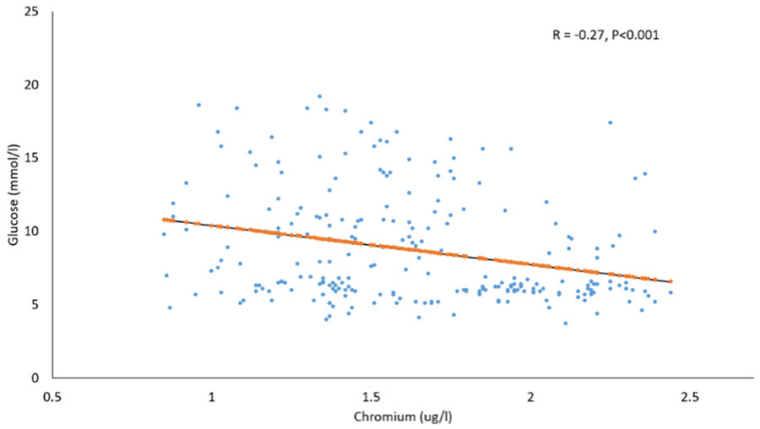

Figure 1. Correlation between glucose (mmol/l) and Cr (µg/l) in T2DM and pre-DM patients. Type 2 Diabetes Mellitus (T2DM).

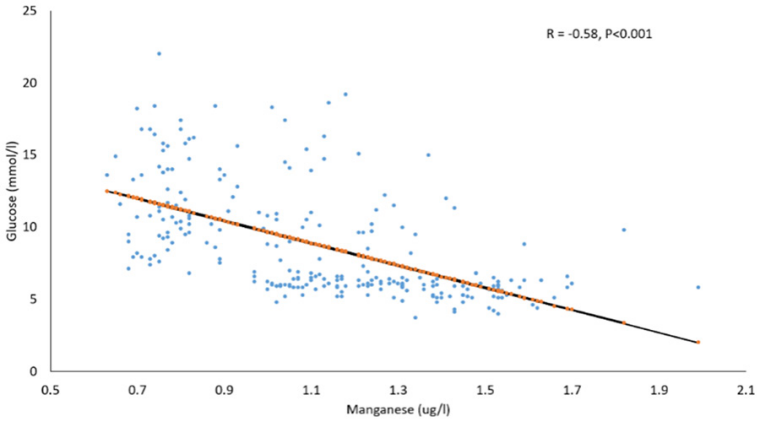

Figure 2. Correlation between glucose (mmol/l) and Mn (µg/l) in T2DM and pre-DM patients. Type 2 Diabetes Mellitus (T2DM), Manganese (Mn).

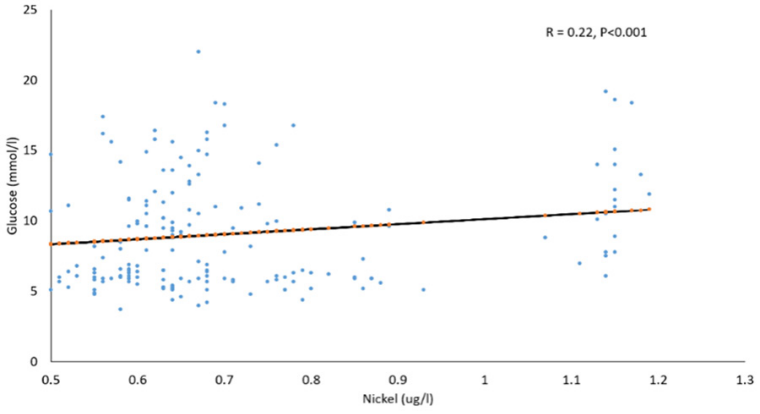

Figure 3. Correlation between glucose (mmol/l) and Ni (µg/l) in T2DM and pre-DM patients. Type 2 Diabetes Mellitus (T2DM), Nickel (Ni).

compared to controls. Serum Se was the only trace mineral whose values varied between pre-DM and T2DM patients, and these were greater in the T2DM group (78.4 g/l) than in the pre-DM group (38.2 g/l).

Scatter plot of glucose (mmol/l) and Cr (g/l) in individuals with T2DM and pre-DM is shown in **Figure 1**. There was a statistically significant inverse relationship between glucose and Cr (R = -0.27, P = 0.001) (**Figure 1**). The relationship between glucose and Mn in T2DM and individuals at risk for developing diabetes is depicted in **Figure 2**. Correlation analysis reveals a moderately inverse relationship between glucose and Mn (R = -0.58, P = 0.001). If you look at the trend line, you'll see that as Mn increases, glucose concentration goes down. Scatter plot of glucose (mmol/l) and Ni (g/l) in type 2 diabetics and prediabetics is shown in **Figure 3**. Coefficient of correlation reveals a positive although weak relationship between glucose and Ni [R = 0.22, P = 0.001]. As Ni levels rise, the trend line also indicates a little uptick in glucose concentration. Patients with T2DM and pre-DM are shown in **Figure 4**'s scatter plot of glucose and Se. There is a positive but weak relationship between glucose and Se, as shown by the positive and significant value of the correlation coefficient [R = 0.20, P = 0.001].

Discussion

The present study shows that serum concentration of Cr in the pre-diabetic group was significantly higher than the median of normal [1.8 vs. 1.6 µg/l, P<0.05] and T2DM [1.8 vs. 1.5 µg/l, P<0.05] groups. Likewise, no significant differ-

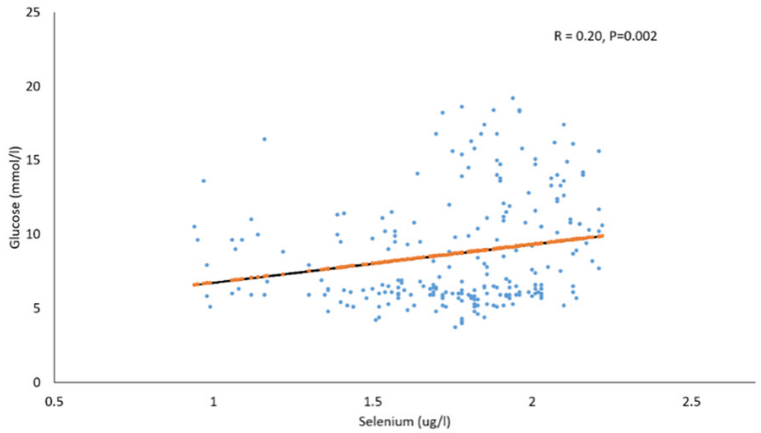

Figure 4. Correlation between glucose (mmol/l) and Se (μg/l) in T2DM and pre-DM patients. Type 2 Diabetes Mellitus (T2DM), and Selenium (Se).

ence was found in serum for T2DM and normal group [1.5 vs. 1.6, P<0.05]. Most studies that investigated the level of Cr in serum of T2DM patients demonstrated that it was lower when compared with non-T2DM controls [4, 13, 14, 26, 27]. In addition, the levels of Cr deficiency are relatively common in patients with pre-DM [28]. Insufficiency of Cr in T2DM patients will lead to alterations in metabolism of Cr by lower absorption, along with an inadequate dietary intake, and higher loss [14]. The prolonged high-level increment of glucose in blood may cause an increase in the osmotic pressure of kidney tubules that impair the kidney function to water reabsorption resulting in polyuria and excretion of Cr by the urine [14, 23, 27]. Some reports show that supplements of Cr lower the level of blood sugar in T2DM patients [29] which may help to scale back levels of glucose, lipid peroxidation and oxidative stress in T2DM subjects [14].

The results in this study indicate that serum levels of Mn in the diabetes group was significantly less than the median of the control [6.6 vs. 28.1 μg/l, P<0.05] and pre-DM [6.6 vs. 14.8 μg/l, P<0.05] groups. Furthermore, median Mn concentration was also higher in pre-DM as compared to T2DM group [14.8 vs. 6.6 μg/l, P<0.05]. Our results agree with findings of other researchers [13, 14, 23, 24, 27, 28] who found that serum concentration of Mn was decreased in T2DM patients in contrast with control. Also, there is study which shows reduced Mn concentration in pre-DM subjects as compared to controls [30]. The significant role of Mn in the action of insulin is to activate enzyme hexokinase therapy increasing glucose entry into cells and its deficiency can reason hypoglycaemia [13]. A study by Eva et al., 2016 shows that Mn deficiency may come with diabetes-related complications [30]. T2DM complications result from increases of oxidative stress in T2DM patients due to Mn deficiency, which produce less protection from oxidation of low-density lipoprotein (LDL) cholesterol. This oxidation of LDL leads to an accumulation of plaque in intra-arterials that will cause heart attack and stroke [30]. The concentration of Mn elimination by the urine was observed to be notably higher in the T2DM patients than controls [4, 26]. This finding concurs with the work of some authors, who indicated the lower blood Mn levels in T2DM subjects might be a result of increased urinary excretion of Mn [27]. Mn supplementation may increase the activity of the Mn-SOD and reduce possible T2DM complications [31]. It is important to recognize that exposure to Mn should remain low and should not exceed what is normally found in the diet [32].

The findings of this study indicate that the serum concentration of Ni in patients with pre-DM was substantially lower than controls (3.5 vs. 4.4 g/l, P < 0.05) and patients with T2DM (3.5 vs. 4.4 g/l, P < 0.05). Also, there was no significant difference seen between patients with T2DM and control subjects (4.4 vs. 4.4 g/l, P < 0.05). Forte et al. (2013) concluded that T2DM is linked to a low concentration of Ni in the blood when compared to control subjects. This was a non-toxic level of Ni in T2DM, which can be interpreted as protective effects against the onset of diabetes, in particular against diabetes glucose deregulation [11]. In their study published in 2015, Liu et al. reported for the first time that T2DM Chinese individuals' urine Ni levels were rising [18]. On the other hand, there were no significant differences discovered between the serum Ni levels of T2DM patients and controls [33].

The outcomes in this study show that serum concentration of Se in the T2DM group was notably higher than the median of pre-DM [78.4 vs. 60.1 μg/l, P<0.05] and normal [78.4 vs. 55.7 μg/l, P<0.05] groups. There are a lot of studies that established the association of trace elements and the risk of T2DM, in which they found increased serum se levels in T2DM patients [19, 34-37]. Zhang et al., 2017 showed that the serum Se concentration was positively correlated with polyethylene glycol (PEG), fasting blood glucose (FBG), and HbA1C. They also showed that remarkably the serum Se concentration increased in participants whose HbA1C>6%, which suggested that high serum Se levels are associated with hyperglycemia [19]. There is a small risk with the increase of Se levels that is of possible public health importance because of the high incidence of DM and the pervasiveness of Se exposure [36]. Among Chinese adults, Se was positively linked with incidence of T2DM [36]. The association of insulin resistance to Se and T2DM could be a consequence of pathophysiological changes [38]. More research is needed to determine the role of high Se levels in the progression or the development of T2DM [35]. There was no big study that compared T2DM patients with non-T2DM in both serum Se concentration and insulin resistance [38].

Deficiencies in trace minerals may have a role in altering glucose metabolism homeostasis, and the change of metals status can induce oxidative stress that may participate with insulin resistance and development of diabetic complications. Results demonstrated that T2DM is related to both, low concentration of Mn and to high level of Se. In this regard, supplementation of this element in patients with low blood Mn levels may be necessary to restore normal levels of insulin synthesis and secretion by increasing Mn-SOD activity. The results showed that subjects with T2DM had a baseline concentration of Cr and Ni in their blood, and that there is no correlation between these metals and the risk of developing diabetes.

Conclusion

Findings of this study suggest that several trace elements may have a role in the etiology of T2DM and as such, knowing the status of trace elements among individuals at risk may have clinical implications. Appropriate supplementation of dietary minerals is encouraged in high risk populations.

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Disclosure of conflict of interest

None.

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